AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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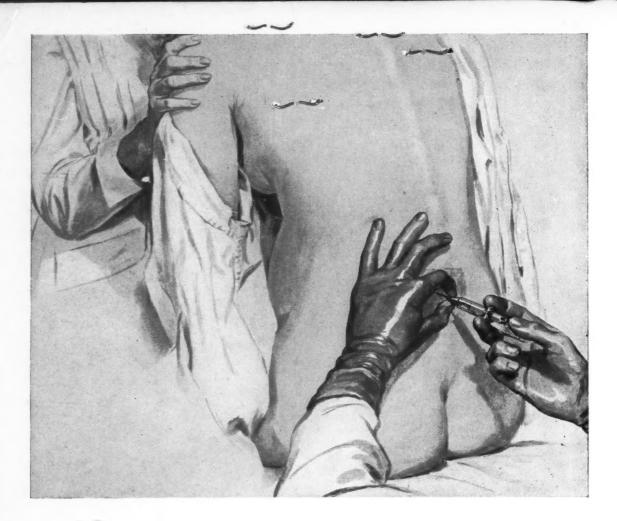
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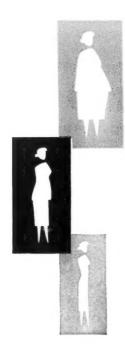
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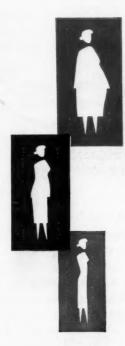
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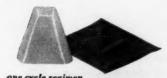
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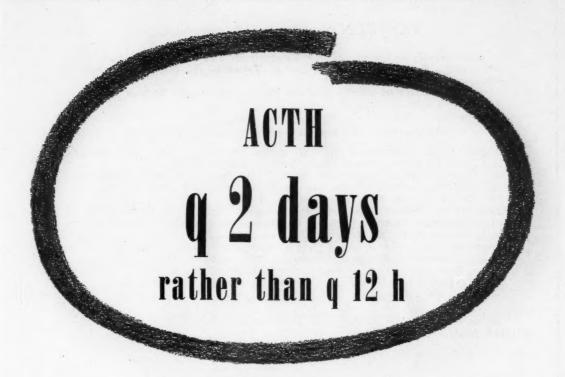
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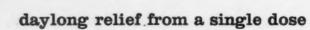




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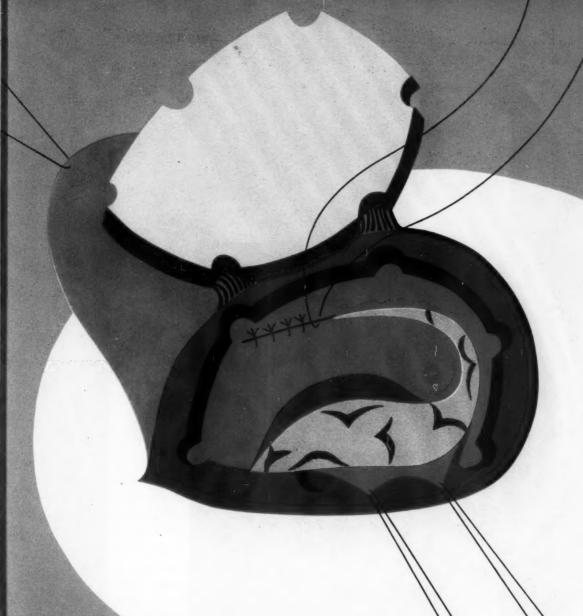
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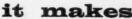
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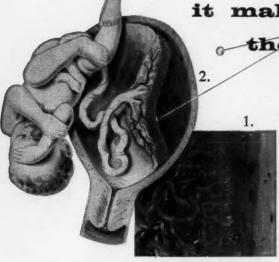
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REFERENCES

- 1. Dill, L. V., Med. Annals of D. C. 23:12, 1954
- 2. Greenblatt, R. B., Obst. & Gyn. 2:5, 1953
- 3. Javert, C. T., Obst. & Gyn. 3:4, 1954





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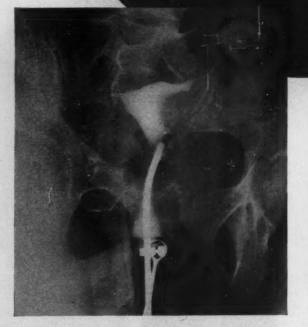
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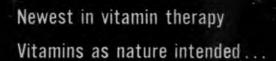
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ITS CAUSES	ITS EFFECTS
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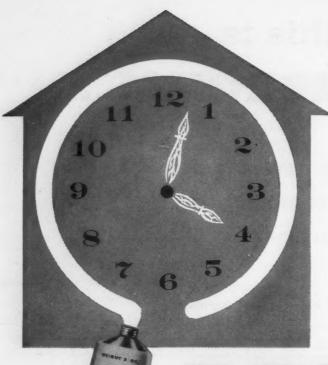
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Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
 Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
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 Turell, R.: New York St. J. M. 50:2282, 1950.

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- 1. College Study Report: Population Bulletin 11:45 (June) 1955.
- Tietze, C., in Dickinson, R. L.: Techniques of Conception Control, ed. 3, Baltimore, Williams & Wilkins Co., 1950, pp. 55-57.

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prophylaxis for narcotic-induced apnea



MAJOR ADVANTAGES: In therapeutic dosage, quickly boosts minute volume and respiratory rate 200 to 300 per cent; does not induce convulsions.

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REFERENCES

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 Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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pain relief plus antibacterial therapy

In cystitis, prostatitis, urethritis and other urinary infections, Azo Gantrisin 'Roche' provides:

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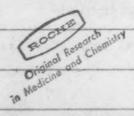
Each Azo Gantrisin tablet contains 0.5 Gm

Gantrisin 'Roche' plus 50 mg phenylazo
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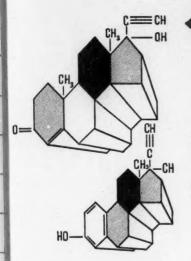
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-Gardner, F. H.: J. Lab. & Clin. Med. 41:56 (Jan.) 1953.

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-Holly, R. G.: Obst. & Gynec. 5:562 (April) 1955.

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-Hill, J. M.; LaJous, J., and Sebastian, F.J.: Texas J. Med. 51:686 (Oct.) 1955.

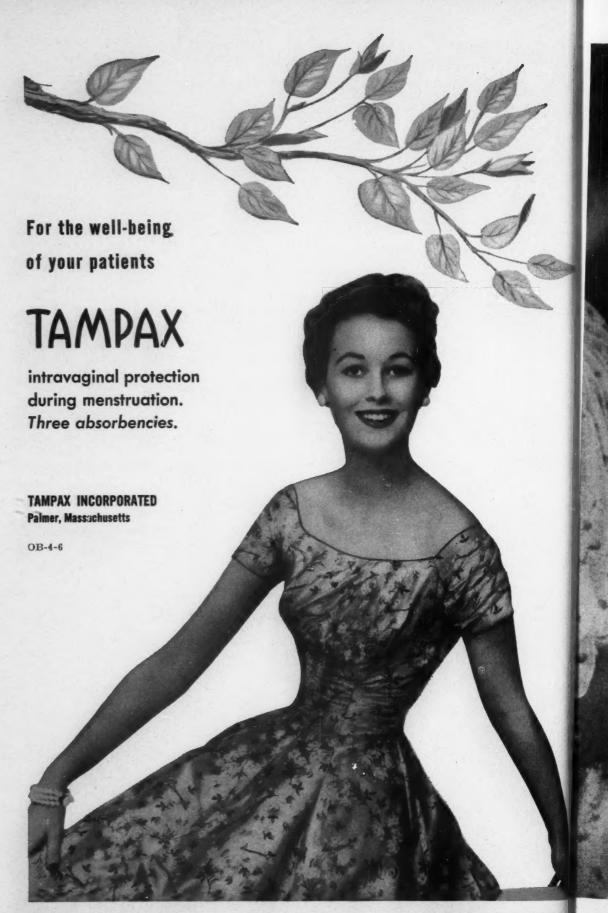
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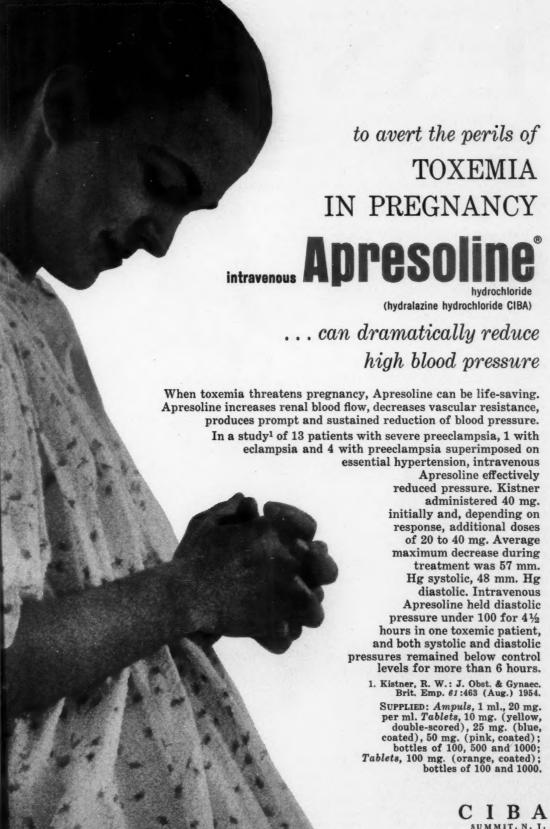
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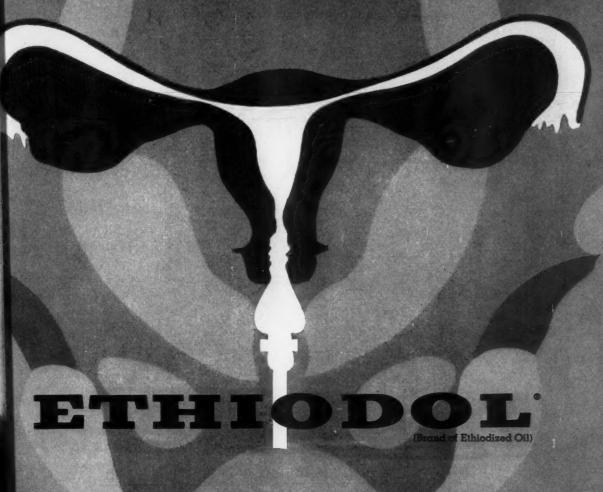
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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, T Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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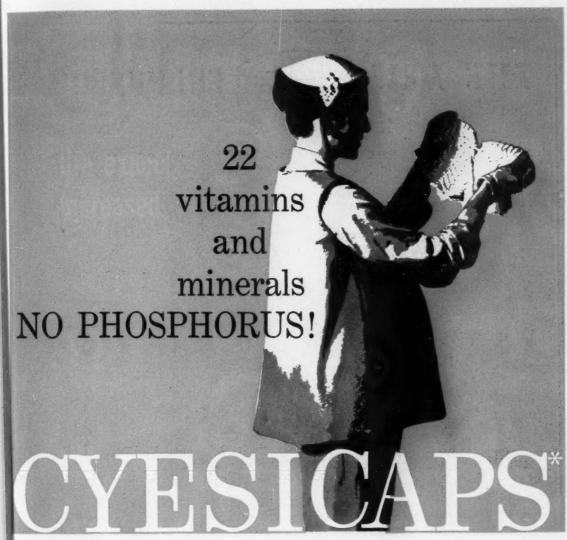
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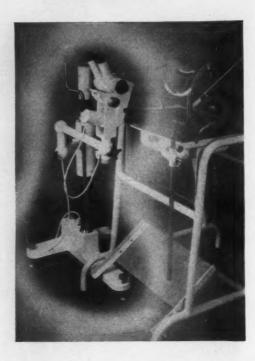
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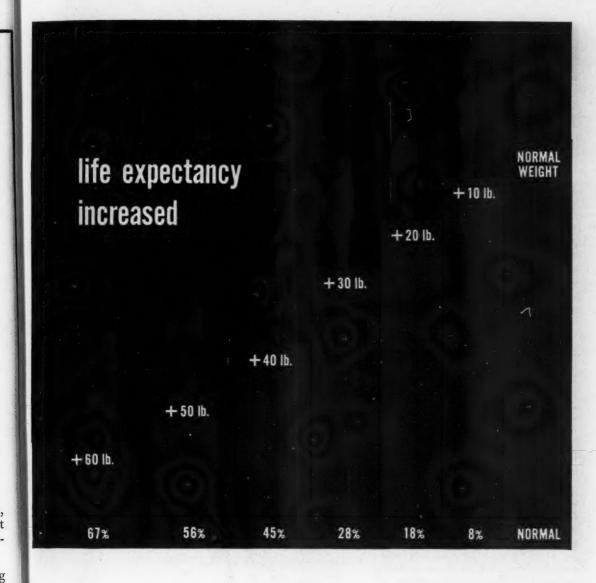
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in the Ideal Reducing Diet

In reducing, the primary consideration is the establishment of a negative caloric balance as well as the maintenance of an optimal nutritional state in the obese person. For achieving this objective "the ideal reducing diet . . . not necessarily devoid of any food present in the normal diet" includes "meat, poultry, fish, eggs, milk, and other dairy products, leafy green and yellow vegetables, citrus fruits, and enriched and whole grain products . . . all desirable and necessary" foods.*

High in palatability and high in many nutrients, enriched bread helps notably to make the reducing regimen appealing and adequate nutritionally. In so doing it helps "to assure weight reduction without irritability and personality change" as well as "to avoid self defeat due to physical weakness and consequent inactivity."* Furthermore, the "ideal reducing diet" makes for increased likelihood of a permanent change from excessive eating to normal food habits "tuned to self control rather than outright abnegation."

The table presented below shows that 4 to 6 average slices of enriched bread serve to good advantage nutritionally in reducing diets. Providing generous amounts of protein, B vitamins, and minerals, enriched bread goes far toward making the low caloric regimen adequate in these nutrients. Its protein, containing an average of 10.5 per cent of milk protein, functions for growth and repair of tissues as well as for maintenance. Fresh or toasted, or as tasty sandwiches, enriched bread provides eating satisfaction, an essential for making the reducing regimen



Contribution of 6 Slices of Enriched Bread

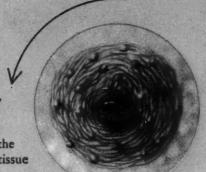
	Nutrients and Calories	Percentages of Allowances**
Protein	11.7 Gm.	18%
Thiamine	0.33 mg.	22
Niacin	3.0 mg.	20
Riboflavin	0.21 mg.	13
Iron	3.3 mg.	28
Calcium (average)	122 mg.	15
Calories	379	13

*Berryman, G. H.: Obesity—A Brief Revis of the Problem, Metabolism 3:544 (Nov.) 195

**Percentages of daily allowances for fair active man 45 years of age, 67 inches height, and weighing 143 pounds: Reco mended Dietary Allowances, Washingto D.C., National Academy of Sciences—Nation Research Council Publication 302, 1953.

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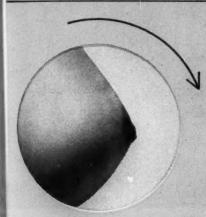
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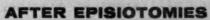
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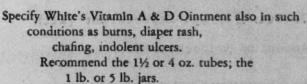


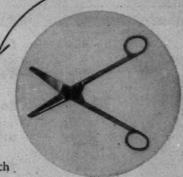
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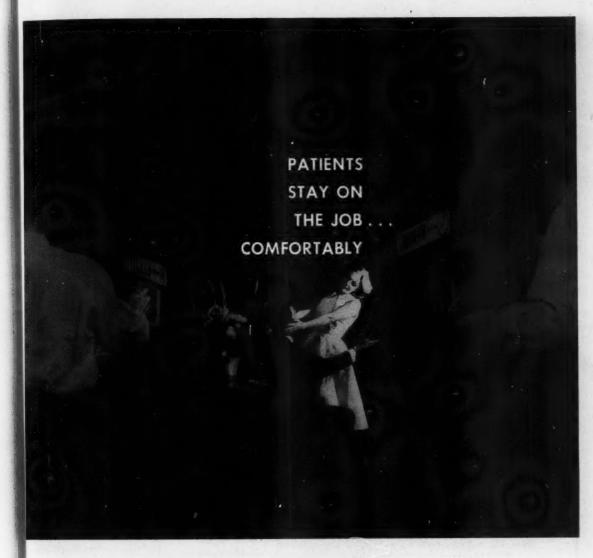
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American Journal of Obstetrics and Gynecology

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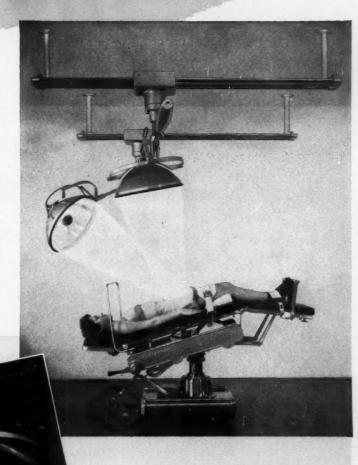
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"Fight Cancer with a Checkup" is the American Cancer Society's immediate, shortrange answer to the terrible toll of lives taken each year by this dread disease. It is to your office that the Society is urging the public to go for the periodic examinations that can mean the early detection and prompt treatment of cancer, and could prevent thousands and thousands of needless deaths.

Achievement of our ultimate goal – the conquest of cancer – will be largely determined by the response to our plea to "Fight Cancer with a Check". This year the Society needs \$26,000,000 to carry on its vital program of education, research and service.

"Fight Cancer with a Checkup and a Check"—a winning combination. With your support and the cooperation of the public, the sound of victory will one day ring through the land.

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1. Groskloss, H. H. et al.:
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Doyle, J. C.: California Med. 71:15 (July) 1949.
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ngblood, V. H.: J. Urol. 70:926, 1953.

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A Laboratory and Clinical Report on Adrenosem® Salicylate

(BRAND OF CARBAZOCHROME SALICYLATE)

History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam¹ in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"2 enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well.... One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.2-7

Sherber, in an early study,3 concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted and is superior to any similar material that is now available."

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He continues, "From our experience it ap post pears that adrenochromazone complex is indiregion cated in preventing vascular accidents incident that to hypertension; in maintaining small vesse ate integrity; in the preoperative preparation bleed where oozing from a vascular bed is antici esop. pated, as in tonsillectomies, adenoidectomic hemo and prostatectomies; and as an adjunct in the gions treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered tients simultaneously (but separately) with any typ of anesthetic, anticoagulant, or vitamin and heparin.

A Unique Systemic Hemostat

Clinical investigators2-7 are in agreemen benefit that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeabilit and by promoting the retraction of severe It has capillary ends. It aids in maintaining norm bleedi capillary integrity by direct action on theional intercellular "cement" in capillary walls. The menor interesting work of Fulton8 confirms thi and p Adrenosem Salicylate, since it is not a vas tion, a constrictor, has no effect on large sever during blood vessels and arterioles.

Adrenosem Salicylate is being used boldide] prophylactically and therapeutically in tho sands of hospitals, and in virtually every typended of surgical procedure. It has also proved morree fro useful in dental surgery.7

Owings reported on the use of Adrenose THE Salicylate in controlling postoperative adent EW Y bleeding in 102 cases.4 "We have used 21/2 m

(* U.S. Patent 2,581,850)

(1/2 ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from mor previous records, without Adrenosem Salicylthe ate medication.

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Peele reports on the use of Adrenosem Saliat i cylate in treating 178 patients with 24 different conditions.⁵ The drug was first used to control t ap postoperative hemorrhage from the adenoid indiregion. He adds: "The results were so dramatic iden that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchontici esophagolic procedures, to treat postoperative omie hemorrhage from the tonsil and adenoid rein the gions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate gica in controlling bleeding and oozing in 330 pastere tients is reviewed by Bacala.6 "Our experience y typ of the effect of carbazochrome salicylate on nin k 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely emer benefited by this metabolic hemostat, making eeding diminution of the control incidence of postcabilit tonsillectomy bleeding of 19.8% down to 7%. severent t has also been found useful in gastro-intestinal norm bleeding, cataract extraction, epistaxis, incion thional seepage, trans-urethral prostatectomy, lls. The menometrorrhagias, cervical ooze, antepartum as thi and postpartum bleeding, threatened abora vastion, and prevention of capillary hemorrhages sever during hedulin or dicumerol therapy."

ed bo Side Effects

n thou All investigators concur that, at recomery tymended dosage levels, Adrenosem Salicylate is red molfree from toxic effects. No cumulative effects attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."5

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with: tonsillectomy, adenoidectomy and nasopharynx surgery; prostatic and bladder surgery; uterine bleeding; postpartum hemorrhage; dental surgery; chest surgery and chronic pulmonary bleeding.

Dosage

For recommended dosage schedules, please send for detailed literature.

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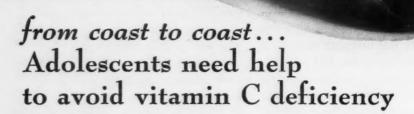
- Ampuls: 5 mg., 1 cc. (package of 5).
- Tablets: 1 mg. S.C. Orange, bottles of 50.
- Tablets: 2.5 mg. S.C. Yellow, bottles of 50.
- Syrup: 2.5 mg. per 5 cc. (1 tsp.), 4 ounce

bottles.

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Typical reports from nutritional surveys show: Among 780 junior high school students in Maine, two-thirds of the boys and one-half of the girls eat diets deficient in vitamin C.¹

Teen-age boys in Iowa neglect foods rich in vitamin C while girls stint on all foods to keep fashionably slim.²

Daily meals of students in four colleges of the Pacific Northwest provide inadequate vitamin C more than 60% of the time.³

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American Journal of Obstetrics and Gynecology

Vol. 71

APRIL, 1956

No. 4

Transactions of the Eleventh Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada

THE ESTABLISHMENT OF A NEW MEDICAL SCHOOL*

Presidential Address

ALEC M. AGNEW, M.D., VANCOUVER, B. C.

(From the Department of Obstetrics and Gynaecology, University of British Columbia)

The establishment of a new medical school on this continent in our lifetime, has been, to say the least, a rather sporadic occasion. To have watched the development and attended the birth of the new medical school of the University of British Columbia has been of tremendous interest and extremely enlightening, particularly to myself, long parted from intimate association with undergraduate medical education. This was a really primiparous experience; in the words of King Lear, there was great fun at the making, a thrilling conception. Only after being firmly nidated in this new environment and daily seeing the rapid proliferation and the innumerable complexities of growth factors in this new organism, did I, like the foolish virgin, have some qualms as to the ultimate outcome of what had seemed in the beginning a most glittering prospect. Through the period of inevitable readjustments, the sour eructations have been followed by benevolent digestion, the periods of rapid internal growth and turbulence have been followed by periods of calm and quiet. Emotional storms of fear and fright, brought about by the rapid growth

*Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynae-cologists of Canada, June 17, 18 and 19, 1955, Huntsville, Ontario.

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of an unknown quantity, made terrifying the prospect of what might be brought forth. The storms passed, lightening occurred, and the results of these labors came into being.

Ours was not exactly a precipitate birth. Some forty-odd years ago, when the University of B. C. was established, the man chosen to be its first President was Dr. Wesbrook, a doctor of medicine. Among his many ambitions for this new University, in a young province, was a specially cherished one, that of the establishment of a medical school. In this respect, there followed a prolonged period of incoordinate activity, long intervals of extreme inertia, interspersed with occasional periods of spasmodic activity, also one or two painful colicky episodes which became almost pathological. Time, however, with its benevolent sedation, as so often happens, eventually brought about a proper gradient of coordinate activity and, though this was also painful at times, the pains were productive; at last the long period of inertia was ended, the new medical school was born.

As obstetricians and gynaecologists, we are all particularly interested and gratified when we contemplate the advances that have been made in a more basic and scientific understanding of our favorite subjects, and proud indeed when present statistics of maternal mortality and morbidity are periodically reviewed and published in our professional journals and in the lay press. And well we might be, for they tell a laudable story of progress. What is less laudable, however, is the fact that, in the long struggle throughout the world toward a reduction in the fearful hazard of childbirth, one of the great obstructions to progress has been the attitude of our profession at large, who looked upon childbirth, when they looked at all, as that annoying physiological process which was better left alone and conveniently ignored, a typically male attitude of superiority and indifference to woman, in circumstances peculiar to her. How consistent is the male animal; history and literature through the ages are filled with references to the barren woman, no mention ever being made to any such plague affecting the male—his prowess is never questioned.

Too great a remnant of this same attitude still exists, and one still too frequently hears from members of our profession the same phrase, "a purely physiological process." The medical man, despite having cast aside his skins and horns and rattling gourds, the surgeon having dispensed with his barber's pole, still experience a great amazement, when contemplating the clock hours in medical education, to find that some of this time which is rightfully theirs has been wantonly misappropriated for the study of a process beneath the superior dignity of man. Just as medicine has broken out of the rigid shafts of the horse and buggy era, so has obstetrics come out from beneath the sheets of primitive superstitions and practices. Medicine advances today, as the gap closes between the medical sciences and clinical medicine. The clinician has become a close partner of the medical scientist and the result is a happier one as evidenced by the steadily improving health and longevity of the community. The old division of medical education into two separate entities, the preclinical years and the clinical years, is rapidly becoming of historical interest only.

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In our new medical school, the teaching of obstetrics and gynecology is combined in one department, and I would like to give you a brief and rather cinemascopic view of the program which I hope will be of interest, as the great distances which separate us make personal visits and firsthand surveys difficult.

All clinical departments are centered at the Vancouver General Hospital, the heads of the four major departments are full-time professors and are heads of the corresponding departments in the Hospital, where the greater part of the teaching program is carried out.

In the Department of Obstetrics and Gynaecology we receive each class for the first time in their second year, and during the second term of this year they are given a course of 18 lectures, which is a course in the physiology (in its broad sense) of conception, pregnancy, labor, and the puerperium. Throughout this course, the clinical connotation is consistently pictured, so that their newly acquired and extensive knowledge of anatomy, embryology, chemistry, and physiology may begin to take on a new and more exciting form. Clinical teaching in obstetrics must be on a sound and thorough foundation of the physiology of obstetrics in all its aspects. In spite of all that is said and written of this age of specialization, it is still a fact that the majority of each class are going to end up in the practice of general medicine, and it is also still a fact that the greater percentage of mothers will be taken care of through their pregnancy and labor by this same majority. Upon medical education lies the responsibility of providing this foundation and creating a wider and wider interest in obstetries, so that the great gains in maternal mortality and morbidity may not only be maintained, but steadily improved.

During the third year, the students receive both didactic and clinical teaching. The year is divided into two equal terms. In the first term they receive a course of 34 lectures covering the abnormalities of conception, pregnancy, labor, and the puerperium. Also during the first term each student, in groups of five to one instructor, receives for a period of eight weeks clinical instruction covering normal obstetrics, his time being equally divided between teaching in the outpatient department and teaching in the manikin room, the ward, and the delivery room.

In the second term a course of lectures is given in gynecology, and also in this second term each group of five students, having completed their course in didactic lectures in obstetrics, return for another eight-week period of clinical teaching, covering the pathology or abnormalities of conception, pregnancy, labor, and the puerperium.

In teaching, and possibly to a greater degree in clinical teaching, one of the hazards is undoubtedly student fatigue and resulting loss of interest; but a much greater hazard is that of teacher fatigue and boredom. When an individual clinician meets eight to ten small groups of students, in the course of each year, and on two, three, or four occasions repeats to each group the same things, on the same subject, and again the same thing year after year, it is not too difficult to understand the development of a state of chronic boredom in the teacher, which is quickly evident as a reflection in the student. In an attempt

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to avoid this hazard in the instructor, and to stimulate and maintain interest in the student, each instructor has the same clinical group throughout the first term and again throughout the second term. He covers a prescribed series of topics, which means that over the year he takes a group whom he comes to know, each by his first name, through a complete clinical course of normal and abnormal obstetrics. This has undoubtedly made for greater personal interest on the part of the clinician and a feeling of contributing in a more complete sense to the student's knowledge.

In the fourth or final year, each student comes to us for a block time of five weeks. In groups of ten, they live in a students' dormitory in the Women's Pavilion, which by some strange coincidence is directly across the corridor from my own office. They are assigned on an organized service during this period, on a similar basis to the intern with whom they are closely associated, and deal with both ward or teaching patients, as we refer to them, and semiprivate patients. Their regular weekly schedule includes daily rounds with the resident staff, three times a week with the junior staff clinician, and weekly rounds with the head of the service; weekly clinics with both myself and my full-time associate; and two pathological conferences each week, one the current obstetrical and gynecological pathology of the Hospital, the other the current pathology of the Cancer Institute, with the presentation and examination of patients. They attend outpatient clinics four afternoons a week, and once a week a clinicopathological conference on problems of the newborn, put on by the resident staffs of the Department of Obstetrics and the Department of Paediatrics.

One of the great disadvantages of the block time system of teaching in the final year of medicine, which existed in my time as a student, and which from my observations in many schools has changed very little, is that of receiving a very concentrated dose of one subject at a time, and then having it completely drop out of sight because of the concentrated pressure of the next dose, and hearing or seeing nothing of it again until spring examinations rear their ugly head. Also, the subject the student happens to have during the last block of the year suffers horribly from not only spring fever, but the fever created by the rapidly approaching final examinations.

To keep a constant contact between obstetrics and the whole class throughout the final year, to maintain interest and add to their teaching, and to reduce to some extent the frantic and panic-stricken efforts of the final weeks before examinations, a Clinico Pathological Conference is held at the end of each week. The presentations at these Conferences are made by the students who are living in on the obstetrical service. The topic of all presentations is based on current cases which are presented, and also includes on the part of the student a review of the current literature on the subject. Two students take part each week; they are permitted to use limited notes only in giving their presenation and they also carry on with the answering of questions and the discussion brought up by members of the class during the period allotted for such discussion. These conferences are very popular, the questions many and pertinent, and the discussion stimulating. A high standard of presentation has

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resulted from a natural and friendly feeling of competition, and we feel it is a very valuable form of teaching and serves the original purpose well.

All obstetrical patients in the Hospital, irrespective of their status as ward patients, semiprivate, and private, are in the one building, the Women's Pavilion, and eventually arrive on the one delivery floor. To take advantage of this large potential, members of the visiting or courtesy staff, selected because of the number of cases they admit and the high quality of their work, were approached beforehand as to a contribution to the teaching program. The result is an interest in the student on the part of such men, with a great gain to the student in added experience, in a form which might be considered as an internal apprenticeship. Many of these members of the visiting staff keep in close touch with the department through attendance at a weekly clinical conference put on by the staff, which is open to all, and a three-day refresher course in obstetrics and gynecology put on each year. This also plays an important part, in these days of high interest in the question of general practitioner relationships and the widespread interest in the Academy of General Practice.

To the development of prepaid medical plans and hospital insurance has been added, at least in our Province, Social Assistance medical services, through which the Provincial Government makes a per capita grant to the Medical Association, by which medical services to the indigent patient are paid for, on a percentage basis, which works out to approximately 50 per cent of the minimum fee schedule.

You are all aware of the effect of all such social legislation on medical education, and in many centers it has been a cause for great concern and undoubtedly many modifications and changes will have to be made, now and in the future. We have found in the development of a new school under present social conditions that a great volume of teaching material can be used in clinical teaching among patients who are now classed as semiprivate and private under those schemes without any insuperable difficulties, and admissions to our outpatient department have not fallen off.

Between graduation and the beginning of internship, for a period of six weeks, an apprenticeship on a voluntary basis has been arranged with selected men in general practice throughout the Province. Opinion differs as to the value of such apprenticeship, but the 50 per cent of the first class who took advantage of this arrangement have been enthusiastic, almost without exception.

It is the policy, when economic circumstances permit, to encourage the new graduate to do his internship in some other center. This policy comes about more easily in a new school where the members of the teaching staff come from many and far-flung centers of medical education. I hope this continues, for, to the individual in his lifetime in the practice of medicine, few things are of greater value than travel. The contact with people in other places widens his horizon and deepens his scientific knowledge and, of equal importance, his insight into the humanities, all of which will be reflected in his lifetime of practicing the Art and Science of Medicine.

THE ROLE OF MAJOR SURGERY IN INFERTILITY*

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THE majority of patients who present themselves to us with fertility problems are found on examination to have no abnormal physical signs and on further investigation to have no evidence of organic disease. In a very small minority physical examination or subsequent investigation may reveal evidence of organic disease, with or without any associated symptoms other than infertility. It is about this very small minority that I wish to speak today. This is not because I or anyone else has an overwhelming experience in such problems, because they are relatively uncommon in our daily work, but because they present problems to us when they do occur, which call for the exercise of the most careful clinical judgment.

If surgical intervention is decided upon, often the highest degree of technical skill that we are called upon to practice is essential for success. None of us, probably, can quote from hundreds of cases of salpingostomies or myomectomies as we can hysterectomies or repairs of the pelvic floor, but we are all called upon from time to time to give an opinion about the merits or demerits of operative intervention, and it is very often as important to know when not to operate as when to operate. We can sometimes be carried away by surgical enthusiasm into performing an operation against our better judgment in the hope that we may help our patient achieve her ambition of a baby, or at any rate in the hope that the patient may feel, if she has an operation, that everything possible has been done. The problems of infertility in general provide larger scope for experimentation, legitimate or illegitimate, than most others, and I think I am right in saying that the literature seems to contain an everincreasing number of operations devised to help the infertile woman.

This small group of patients with unsuspected organic disease, complaining primarily of infertility, may present in one of several ways. In the first place their organic disease may have given rise to no symptoms at all and may be discovered during the course of routine examination or investigation. Or, second, the patient may have certain secondary and not very severe symptoms which were not, however, her primary complaint. Or, third, the possible effect of the organic disease in relation to fertility may not already have been put to the test, but one is called upon to exercise judgment about the possible effect in the future.

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^{*}Address of the Guest Speaker, presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario.

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Today I should like to discuss with you mainly, problems in relation to fibroids, endometriosis, and pelvic infection, together with certain other less common conditions affecting the uterus. As I have indicated, I cannot produce very large series of figures, but I can give you my experience as far as it has taken me, and indicate the general principles upon which I work.

Fibromyomas

In England, as everyone knows, Bonney was for many years the champion of conservative myomectomy and his figure of 38 per cent of women who become pregnant after myomectomy has been quoted on innumerable occasions. But what is the real significance of this figure in relation to the problem under discussion? How often do we find the pregnant woman in the antenatal clinic with fibroids in the uterus? It is indeed a commonplace, and so one must pose the question: Do fibroids in point of fact ever actually cause sterility, as distinct from being merely associated with it?

We know really very little about the exact causation of fibroids, and the fact that several research workers have produced fibroids in guinea pigs by the injection of an estrogen for periods varying from two to ten months does not really carry us a great deal further. Estrogens produce diffuse hypertrophy of the myometrium, they cause endometrial hyperplasia, they even cause carcinoma of the endometrium or even of the cervix—so we are told. But why and how? All women produce estrogens during the course of their reproductive life—during pregnancy in great abundance—yet only few grow fibroids in the uterus. Pregnancy tends to inhibit their recurrence after removal and to militate against their initial formation. In one woman with fibroids the endometrium may be normal, the ovary may produce eggs at regular intervals, and pregnancy occur with the greatest facility; in another the endometrium may be hyperplastic, the ovary polycystic and ovulation infrequent or totally suppressed, and therefore pregnancy will remain beyond the realms of possibility.

Can we prove that removal of such fibroids will have the effect of changing the function of the ovary and initiating ovulation? If such a thing in point of fact happens, is it due to the removal of the fibroids per se, or is it associated with incalculable nervous, emotional, or other factors following upon a major surgical operation? The cure of infertility may on occasions be achieved by a visit to the doctor's surgery, an examination, and the reassurance that there is nothing organically wrong. It may equally follow an abdominal operation whether it be myomectomy or appendicectomy.

I have looked up the case records of some 60 patients on whom I have carried out myomectomy in the past five or six years. Nineteen (approximately one-third) of them have had babies since the operation, which I think is a reasonable record, especially as a number of the 60 are single women who have had no opportunity of pregnancy. But nevertheless I am not impressed that my operation has really in any way contributed to the successful achievement.

I am afraid that I have not been able to obtain detailed records of all the patients I have seen who had fibroids in their uteri and who have had babies subsequently without operation, but I know they are a considerable band of happy mothers. Perhaps I could quote the histories of 2 patients which will illustrate the point I am trying to make.

The first was a patient who came to see at the age of 35. She had been married for 12 years and had remained without a pregnancy. She was in fact one of Bonney's original 379 patients and she had had 8 fibroids removed by the great man, but still no pregnancy

occurred. When I saw her for the first time she had again 4 or 5 distinctly palpable fibroids, the uterus being the size of a 14 weeks' pregnancy. Apart from her infertility she had no symptoms at all. An endometrial biopsy showed a nonsecretory endometrium, a fact that we confirmed twice subsequently. Not knowing how to cure anovular menstruation but knowing certain things that are credited with doing so, I prescribed a course of serum gonadotrophic hormone. She was pregnant within 3 months and I subsequently carried out a successful cesarean myomectomy as one large fibroid was in the lower segment and would have obstructed labor. The uterus has remained free from the growth of any more fibroids for the last 10 years but she has never managed to achieve a second pregnancy nor has gonadotrophic or other hormone initiated ovulation again as far as we can tell.

A second case I should like to mention was that of a woman who had been married for 15 years and purposely avoided pregnancy. She was 42 when she came to me, because she had noticed a lump in the lower abdomen. She had a fibroid uterus the size of a 14 weeks' pregnancy. I told her I thought a hysterectomy would probably be inevitable sooner or later but that there was no urgency. I did not see her again for a year and then she came for advice because, at 43, she exercised the woman's privilege of changing her mind and now it was a matter of life and death to her that she must have a baby! The fibroid uterus was now a little larger but fortunately not very much so. Here was a problem requiring some thought and judgment. Rightly or wrongly my advice after careful consideration was that if she wanted to have a baby she should go ahead and have it. She duly became pregnant a few months later and I subsequently carried out a cesarean hysterectomy.

These two cases will illustrate the point I am trying to make, that myomectomy should not be looked upon as a rational treatment for infertility. There are of course many indications for this operation during the reproductive years of a patient's life, which we all recognize. In most cases we do the operation in a young woman because the fibroid is causing symptoms and she wishes to retain the uterus for childbearing in the future. We often do it even though it is not causing symptoms but it seems reasonably certain that it will do so because of size or position within a short period of time if it is not removed. And, third, there is the not infrequent case in which a patient has more and more miscarriages for which no other cause can be found than fibroids in the uterus. Here again caution is necessary, and the exact location of the tumor can be ascertained by preliminary hysterography which enables a more accurate assessment of the possible responsibility of the fibroid for the miscarriage. Fibroids may cause miscarriages if they are submucous in position, and sometimes multiple intramural tumors will cause them. But in cases of that sort other more pressing symptoms are usually present indicating immediate operation.

The main point I want to emphasize again is that in the patient complaining only of infertility and in whom symptomless fibroids are found, caution is necessary in relation to surgery, which we are often tempted to undertake.

Myomectomy is an operation with very definite risks which I need not emphasize here, but I am quite sure that we have all seen the cases where myomectomy has been followed by infective complications which have caused and not cured infertility. There is one complication I should like to mention and that is rupture of the myomectomy scar in subsequent pregnancy (Fig. 1). This is an example of silent rupture which occurred at the thirty-second week of pregnancy following myomectomy. It is the only time I have ever seen this complication, and all authorities agree on its rarity. The especial interest in this case was that myomectomy was carried out for a moderate-sized fibroid, but the real cause of the patient's infertility was salpingitis. At the operation I had to remove one tube and ovary completely and I removed a

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large fibroid at the same time. This was one of my relatively few successes with fimbrial salpingostomy and it was a sad disappointment both to the patient and to me that her myomeetomy scar should give way at the thirty-second week and the baby be lost thereby. In retrospect it seems likely that the pelvic infection was the factor causing a weak scar. The myomeetomy scar usually stands up to subsequent pregnancy without undue strain.

In passing I mention conservative resection of an area of adenomyosis. Bonney had no success in the cases he mentioned and in the only case in which I have carried out this operation hysterectomy ultimately became necessary, in spite of the patient's persistent efforts to achieve a pregnancy. A recent case report by Hyams⁷ is of a successful pregnancy following hysteroplasty for localized adenomyosis and there was another by Lock and Myers, ¹⁰ but it must be very rarely called for in practice.



Fig. 1.—Uterus showing ruptured myomectomy scar.

Endometriosis

This is another condition frequently encountered in practice in relation to infertility. Meigs¹³ and other authors have shown the etiological significance of childlessness, of whatever cause, in the development of this condition. Late marriage, voluntary and involuntary sterility, and spinsterhood are all implicated as prime factors causing this disease to develop in the female pelvis so much more frequently than it used to do. But the question that pertains to the present discussion is rather this: Does endometriosis cause infertility, and if it is discovered in a patient anxious to have a baby, should operative treatment be undertaken?

Many authors quote a relatively high incidence of pregnancy following conservative surgical treatment (Meigs 32.4 per cent; Scott¹⁹ 34.4 per cent; Fredrikson²⁰ 38.9 per cent; Counseller nad Crenshaw⁴ 17.4 per cent) to quote

from a few papers that have appeared in the past few years. In most of these patients, however, operative treatment was undertaken because the patient had presenting symptoms more urgent and pressing than infertility, and, because the patients were young and in many cases anxious to conceive, conservative surgery was carried out. No one will seriously question the wisdom of such management. But the problem I am concerned with is the management of the patient whose presenting symptom is infertility and in whom endometriosis is suspected from physical examination or from minimal symptoms.

The incidence of endometriosis in pregnancy is something we cannot ascertain with anything approaching accuracy. A recent report by Gainey and associates gives the incidence in pregnancy as 1.4 per cent, but the authors give no indication as to how they arrive at that figure. We have no doubt all seen patients with ovarian endometriosis who require operation during pregnancy for intractable or acute pain. Fig. 2 shows decidual reaction in the stroma of an area of endometriosis removed during pregnancy. The diagnosis cannot be made with reliable accuracy in the majority of patients in whom the two conditions are associated, however, unless operation is undertaken.

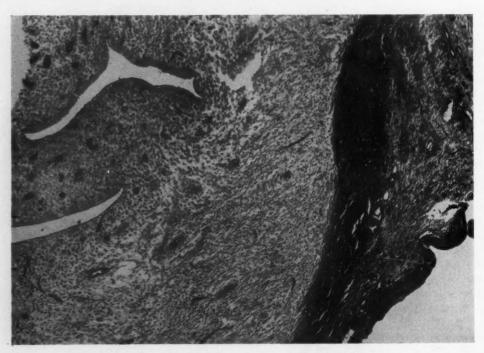


Fig. 2.—Ovary with endometrial tissue showing decidual reaction of pregnancy.

Most gynecologists could agree, I think, that if the condition was suspected in a patient with few or no complaints aside from infertility, operative interference is not justified in the first instance. It is indeed questionable if operative intervention should always be undertaken in the young married woman anxious to have a baby, even in the presence of pain and other symptoms. I need hardly say that all the other possible factors associated with infertility should always be explored before surgical treatment is undertaken, and ample time allowed to elapse for pregnancy to occur. If conservative treatment is pursued, in the hope that a pregnancy will start, both estrogens and androgens have been advocated to alleviate any symptoms the patient may have. The rationale

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behind the use of estrogens is to inhibit the presumed overactivity of the pituitary, but it would be very likely to inhibit ovulation and thereby prevent pregnancy. Testosterone, on the other hand, may inhibit the pituitary, but I think it appears to have some direct action on endometrial tissue as well as exerting an influence through ovarian function. It is for that reason that I prefer its use in patients anxious to conceive. It appears to reduce pain and blood loss, without necessarily interfering with the menstrual cycle or preventing pregnancy.

The clinical history of a fairly recent patient of mine is worth recording in some detail because of the gross degree of endometriosis from which she was suffering.

When I first saw her she had what amounted to a nearly frozen pelvis with endometriosis, confirmed histologically and sprouting through the posterior vaginal fornix. Her age was 32 and she had never conceived in 6 years. She had suffered quite intolerable pain during her periods for about a year previously but she absolutely refused any form of radical surgery. I was persuaded to operate on her with a view to doing some conservative procedure, but this was one of the few patients in whom it was quite literally impossible to do anything except radical removal, that seemed worth while. What I did was simply to dissect free the fimbrial ends of both tubes which were buried in adhesions, drag forward the uterus, and shorten the round ligaments. Big doses of testosterone were given during the next three months (approximately 1,000 mg. in all) with complete relief of dysmenorrhea and other pains. The large mass in the pelvis decreased very considerably in size, and eight months later the patient conceived. I shall never know whether testosterone, my operation, or Nature achieved the desired pregnancy, but I very much suspect the latter agent as the most important.

Nevertheless, I do believe there is evidence in sufficient amount, both theoretical and clinical, to substantiate the belief that endometriosis affecting the ovary may actually cause infertility. This cannot be common and a recent report on 1,032 childless women by McGoogan¹¹ gives an incidence of ovarian endometriosis no greater than 2.3 per cent. The burial of the ovary and its fixation by adhesions, mechanical distortion of the tube and even the obliteration of its fimbrial opening, fixation of the uterine body in the retroverted position may all militate against successful ovulation, migration of the ovum, and cervical insemination. Meigs¹³ stresses the value of ventrosuspension of the uterus after division of adhesions even though total removal of all the involved tissue may not be technically possible in association with the conservation of the essential organs of reproduction. I have been impressed by the frequency with which pregnancy does follow the surgical removal of a localized lesion, whether by resection of a chocolate cyst from one or both ovaries or even total removal of one ovary with partial resection of the other. I can number many of my most grateful patients, as I am sure most of you can, from the group of infertile young women whose infertility has been cured following the surgical excision of unsuspected endometriomatous lesions of the ovary, which has led to successful pregnancy and the arrest, at least temporarily, of the disease process. Nevertheless, I would emphasize again that, in the absence of complicating symptoms such as intractable pain or menorrhagia, operation should not be undertaken before time and conservative measures have been given an adequate chance.

Other Ovarian Pathology

The main problem under this heading is of course the polycystic ovary. This may be associated with anovular menstrual cycles, and if so will inevitably be a cause of infertility. The literature dealing with this subject is very contradictory. Meaker, 12 reporting on 65 patients with polycystic ovaries found

sterility the presenting symptom in 53. He recommends the wedge resection advocated by Stein and Leventhal and claims 66 per cent of the infertile women became pregnant following operation. On the other hand, Carter and coworkers3 reviewed the cases of 500 infertile women and found that in 44 who had unilateral or bilateral polycystic ovaries and who had not been subjected to any operation there was a pregnancy incidence of 40.9 per cent. In 53 who had undergone operative treatment for this condition the incidence of pregnancy was 28.3 per cent. My own experience in the surgical management of this type of case is very limited indeed because I have always been reluctant to carry out an operative procedure that is nonphysiological and offers no valid reason for success. In the few cases in which I have carried out the operation, never for infertility alone but sometimes in patients with other more pressing symptoms as well, I confess to failure in the cure of infertility. It must obviously be an operation that is open to the greatest possible abuse, and very many patients may well become pregnant after the operation, but in spite and not because of it.

Pelvic Inflammatory Disease

Not only is pelvic inflammatory disease the commonest cause of infertility, but at times its preoperative diagnosis is fraught with very considerable difficulties. Within the past few years many papers have been published which discuss the detailed techniques of plastic operations on the Fallopian tubes to restore patency, with varying degrees of success. The pioneers in this field have been Palmer¹⁵ in France, Green Armytage⁶ in England, and many authors on this side of the Atlantic who have published encouraging figures. My own "success rate" based on 48 cases that I have been able to follow up accurately have resulted in 8 successful pregnancies, figures which are in keeping with the general picture obtained from the literature. But I am not so much concerned with figures today. I would like rather to discuss certain aspects of this problem which are very much in need of ventilation, because overenthusiastic surgery undertaken for the relief of infertility resulting from pelvic inflammatory disease is certain to lead to a great many complications without achieving the main purpose for which the operation was undertaken.

1. Diagnosis.—The diagnosis of pelvic inflammatory disease in patients in whom there are grossly abnormal physical signs does not concern us, but the accurate diagnosis of tubal occlusion when no physical signs are present is very much more difficult. Palmer¹⁶ gives figures on the different sites of tubal occlusion. Blockage occurs at the fimbrial end in 52 per cent, in the isthmic portion in 10 per cent, and in the interstitial portion in 32 per cent. We do not know, however, in how many of these patients physical signs were present.

The incidence of 32 per cent cornual occlusion is the figure that is most arresting, diagnosis having been made by hysterosalpingography. It is now well accepted that in those cases where cornual occlusion occurs the causation is usually postabortal or puerperal infection, but in my experience the cases in which this type of tubal occlusion occurs are rare.

In a recent discussion at the Royal Society of Medicine, Bligh and Williams,² quoting their experience at Oxford, stated that of 17 patients who showed cornual occlusion at the first salpingogram, 9 were subsequently shown to have patent tubes. Jeffcoate⁸ states that evidence of bilateral tubal occlusion on salpingography was proved to be fallacious by subsequent pregnancy or laparotomy in 15.1 per cent of cases. I have been able to collect the histories of 12 patients in whom I was unable to demonstrate tubal patency on repeated salpingography who subsequently became pregnant, without operative treatment

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—sometimes remarkably soon after the negative salpingogram. I need hardly emphasize the importance of gentleness, antispasmodics, anesthesia, a warmed solution, and empty bladder and rectum as vitally important.

Personally I have given up salpingography except under anesthesia as I have found a great reduction in false negatives thereby. But there is one point that I do not recollect reading in the literature and that is the necessity for passing the cannula beyond the internal os. There are several types of syringes in common use in England where the point of the cannula does not pass the internal os. I consider that they are virtually useless because it is often quite impossible to obtain an adequate intrauterine pressure with this type of instrument.

I think that the greatest caution and experience are necessary in interpreting the result of salpingography. Operative treatment should never be undertaken for cornual occlusion unless 3 negative salpingograms have been obtained. Even then the tube should be insufflated from within the abdomen before the operation is continued. Finally, histological evidence of interstitial blockage is necessary before organic blockage is proved. Diffiulties in diagnosis apply less forcibly to possible occlusion in the isthmus and ampullary end of the tube; spasm may cause incorrect diagnosis in relation to isthmic blockage, and peritoneal adhesions may give a false picture of the true position at the fimbrial end of the tube. I have personally not been very favorably impressed by the older water-soluble media used for hysterosalpingography in this type of case in which the interpretation of the findings is difficult. Screening is an essential part of the technique and while one may use a water-soluble medium because of its decreased risk initially, repetitions because of equivocal findings the first time should always be repeated with a medium giving a satisfactory contrast shadow. The new water-soluble medium, Salpix, however, appears to be the nearest approach to the ideal that has so far been produced.

2. Pathology of the Tube.—In the literature there appears to be a lack of detailed information about the exact correlation of tubal blockage with the condition of the tube from the viewpoint of health and function of the tubal epithelium and the peristaltic capacity of the tube musculature. More than patency is required for the successful transport of an ovum from the ovary to the uterine eavity.

In practice one encounters three main types of cases:

A. Cornual occlusion with a healthy distal portion of the tube.

B. Fimbrial occlusion with the tube buried in adhesions but the fimbriae relatively healthy even though the tube may be dilated.

C. Club-shaped occlusions of the fimbrial end with complete disappearance of the fimbriae, and the dilatation of the tube.

For obvious reasons the highest success rate will occur in patients in whom the tube is least damaged by the effects of old inflammation. In Group A Green Armytage⁶ recently reported a 40 per cent cure rate in 20 cases following tubouterine reimplantation, and several authors have given results nearly as favorable.

In one of my successful cases the cause of the tubal occlusion was a very unusual one. The patient had one tube and ovary removed for an acute torsion of a cyst, and a ventrosuspension was carried out at the same time by someone who must have been something of a surgical amateur, because the ligature was passed around the remaining Fallopian tube close to the uterine cornu. About half an inch of tube was completely attenuated and had no lumen whatsoever. Uterotubal transplantation has been successful and I am expecting to deliver this patient soon. It would indeed have been disappointing if this result had

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not been obtained, because there was no inflammatory change affecting the mucosa or the musculature of the tube, and the fimbriae and the ovary were perfectly normal.

It would be interesting to know in what proportion of the successful tubouterine implants the tube and ovary were perfectly normal and unaffected by chronic inflammatory changes. Salpingolysis and terminal salpingostomy in cases where the pelvic inflammation arises from outside the genital tract also carry a far better prognosis. Pelvic peritonitis following appendicitis is the commonest cause of occlusion of the tube by such pelvic adhesions, and a similar condition of the tube may be found in some cases of ovarian endometriosis.

In cases of obstruction due to obliteration and destruction of the fimbriae following ascending salpingitis my own experience has been uniformly bad, a point emphasized by Green Armytage, Meigs, and some other authors. It is not indeed surprising that this should be so. In these cases the tube wall may be attenuated and fibrous with most of the muscle destroyed, the secretory function of the tubal epithelium and the ciliae completely destroyed beyond the capability of regeneration. In many of my cases I have been able to demonstrate patency after salpingostomy but patency without restoration of physiological function is quite useless. Any detailed results in relation to plastic operations should be subdivided into their various categories with particular reference to the condition of the Fallopian tube remaining after operation. Only thereby can we hope to select cases more carefully and improve the results in the few patients subjected to these operations.

3. The Condition of the Ovary.—The effect of long-standing inflammatory disease upon the ovary itself is well known. In a great many cases in which it is technically possible to restore patency of the Fallopian tubes the ovary may be so disorganized from fibrosis of its capsule and cystic changes that the liberation of a healthy ovum is impossible. I am sure this accounts for some failures in the operation of salpingostomy.

There is one small point that is worth mentioning in connection with ovarian function. Very often in pelvic inflammatory disease one side is much more affected than the other. I think it is important to view both tubes and ovaries and assess their condition. Very often it is best to discard one tube altogether and in that case it is usually best to discard the ovary as well. I have often been impressed by the frequency with which pregnancy follows the removal of a unilateral tuboovarian swelling, whether due to inflammatory disease or endometriosis, the opposite tube and ovary being healthy, and yet pregnancy not having occurred until the unilateral lesion is totally removed.

Jeffcoate⁹ has recently pointed out the possible advantage of deliberate removal of an ovary even though normal if the adjacent tube has to be sacrificed. He points out that on a simple arithmetical basis at least half the ova produced by the ovaries will fall on barren soil if there is no tube to transport them, whereas, if that ovary is removed, all the ova will be produced by the remaining ovary, thereby doubling the chances of pregnancy. In this case as he aptly expresses it "all the eggs are in one basket." If, therefore, the disease process has become very extensive on one side, it is best to discard that side completely rather than attempt to be conservative on both sides.

4. The High Incidence of Subsequent Ectopic Pregnancy.—This is a very serious danger following all operations undertaken to restore patency to the tubes. Rock and his associates mention 5 ectopic pregnancies following 108 operations; Palmer 4 such pregnancies in 168 patients. These figures do not seem unduly large but expressed in terms of the total number of patients who become pregnant after operation, it is 5 out of 21 in Rock's series and 4 out of

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28 in Palmer's cases. Four of the patients on whom I have operated have had ectopic pregnancies, i.e., one-third of the total pregnancies achieved. These are indeed very high figures, and a grave drawback to the operation. The explanation of this is presumably that poor peristalsis and deficient ciliary action delay the passage of the ovum after fertilization, as well as possible residual areas of relative stenosis. Whether or not the abortion rate is increased is difficult to assess—but one of my successful operations was followed in turn by an abortion, an ectopic, and then a successful pregnancy. It is interesting that the successful pregnancy followed the complete removal of tube and ovary from one side for the ectopic pregnancy two and one-half years after the original bilateral salpingostomy. The patient certainly deserved her baby, that she was very determined to have!

5. Points in Technique.—I have very little to add to the techniques of the various types of salpingostomy and uterotubal implantation that have been described by so many authors recently. There are just three points I should like to emphasize.

A. I have already mentioned the desirability often of choosing the best side and discarding the other in preference to a bilateral procedure.

B. If a polythene or other tube is to be used, and it has many advantages, I think it is best to use a solid polythene bougie rather than a tube which may favor the upward or downward passage of bacteria or infected material.

C. Authors have varied in their views as to whether the tube should be passed through the cervix or brought out through the abdominal wall. I think it is better to avoid both. The polythene tube or bougie can be passed into the cavity of the uterus and left there without being pushed through the cervical canal to lie in the vagina. It requires an anesthetic and dilatation of the cervix in order to remove the tube but this is no serious drawback if ascending secondary infection is thereby avoided.

One last word before leaving the subject of plastic surgery of the Fallopian tube. The time interval between operation and success may be very long—in one of my cases seven years elapsed before the successful pregnancy came—a fact which must give far greater credit to Nature than to surgery.

Operations on the Uterus

Ventrosuspension.—I have little to say about this operation except that I think it should never be undertaken for the alleged cure of infertility, unless it is in association with some of the operations I have been discussing or following the division of adhesions. There is little evidence that a mobile retroverson ever causes infertility and certainly none to justify operation.

Other Operations on the Uterus.—Under this heading I should like to consider briefly the following: transplantation of the ovary (Este's operation); operations for congenital abnormalities of the genital tract and vagina; operations on the cervix.

A. Transplantation of the ovary: Preston¹⁷ recently reported upon 21 patients in whom he had transplanted an ovary into the uterine cavity, both Fallopian tubes having been already removed or being so hopelessly damaged that any form of salpingostomy was quite useless. He records 3 pregnancies in 10 patients he was able to trace. His patients in Nairobi were mostly Kikuyu who are prepared to go to any lengths in order to avoid the opprobrium of sterility. We do not know what happened to the 11 patients who disappeared into the African bush, but 3 pregnancies in 21 cases is quite a triumph of surgery even though the offspring may be potentially Mau Mau!! However, the num-

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ber of cases in which this operation is possible is few—my experience is limited to 2 cases—and in both the ovarian tissue was so disorganized from fibrosis and cystic change that success seemed very unlikely. In one case the patient subsequently developed an abscess in the uterine wall at the site of implantation and hysterectomy became necessary. In the other case, I think the ovary must have sloughed away; following a period of irregular bleeding and discharge, everything settled down but no pregnancy occurred and regular menstruation continued, maintained by the other ovary.

B. Operations for congenital abnormalities: These form a rare but interesting group, but once again operation should not be undertaken until a very full assessment of the case has been carried out. A patient was recently sent to me whose salpingogram showed a simple bicornuate uterus. This patient had been infertile for many years and had been subjected to every conceivable endocrinal exhibition and even had unilateral artificial insemination on alternate months. I was asked to cut out the center piece and join the two halves of the uterus. I managed to persuade the patient who had been reduced almost to a nervous wreck to stop all forms of therapy, to stay away from doctors for twelve months, and told her never to let anyone operate on her uterus. She came back after eight months, pregnant, and her baby is due in twelve weeks' time.

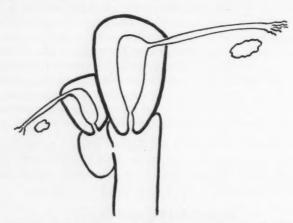


Fig. 3.—Diagram of rudimentary uterus and vagina.

The indications for operating on patients with the congenital abnormalities are few and far between. I think the occasional case of intrauterine septum, usually incomplete, which predisposes to abortion or premature labor justifies surgical removal. I have done this four times with success.

Rarely an undeveloped uterine horn may communicate with an incompletely developed vagina. Fig. 3 illustrates this type of case, which is usually associated with an absent kidney on the same side. This patient has been married for five years without conceiving and the nature and site of origin of the intermittent bloodstained vaginal discharge had escaped detection, as well as the cause of the attacks of pelvic pain. Complete removal of the rudimentary vagina, uterus, tube, and ovary on that side resulted in a pregnancy in a very short time. Also very rarely a septum in the vagina, either transverse or longitudinal, may for mechanical reasons prevent insemination of the cervix which is in connection with a normally developed uterus, tube, and ovary on one side. Its removal obviously cures infertility.

C. Operations on the cervix: The incompetent cervix due to severe laceration of the internal os has been emphasized recently as a possible cause not of in-

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fertility but of habitual abortion. My own experience leads me to believe that this is sometimes the case. In these cases the injury is usually done by forcible dilatation for dysmenorrhea. In one recent case this operation had been done no less than four times without, I may say, relieving the dysmenorrhea. It was possible to pass a No. 10 Hegar dilator straight into the uterus. The patient had 4 abortions in a row after she married and so I felt justified in suggesting operation. Incidentally, hysterography is useful in the diagnosis of this condition. A pregnancy was successfully carried to term in the patient and delivery by cesarean section carried out. Nevertheless it is important to distinguish between what one might describe as physiological rather than anatomical incompetence of the cervix. The former may occur in midpregnancy and predisposes to premature rupture of the membranes and abortion even though the cervix is anatomically completely normal.

Conclusions

Most of what I have said today contains nothing new and I have told you nothing that you did not know perfectly well before. But I have tried to discuss my experience with some of the problems that confront us in the management of the infertile patient. These women are the most anxious, persuasive, and guillible group of patients. Fortunately, only a few of them reach the stage where major surgery is contemplated. But even in major surgery there is just as much scope for overenthusiasm, distorted judgment, and even quackery, as in endocrine or medical therapy. Good judgment, accurate preoperative diagnosis, honesty in prognosis, and careful selection of cases are really more important than surgical technique, if unnecessary and useless operations are not to be practiced and if good results are to be obtained in the few whose only hope of a successful pregnancy depends upon a triumph of surgical skill and above all judgment.

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OBSERVATIONS UPON THE ETIOLOGY AND TREATMENT OF CARCINOMA OF THE CORPUS UTERI*

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WHEN I was a newly qualified resident, in the process of learning about gynecology, we used to be taught that carcinoma of the body of the uterus was a relatively rare form of malignant disease, affecting mainly very elderly patients, a benign type of neoplasm with a very good prognosis from not very radical surgery. Within recent years our attitude to this disease has undergone a slow but radical change, and it appears from what one reads that a similar reorientation of outlook has occurred on this side of the Atlantic. I would like to speak today about certain aspects only of this disease, and I shall speak from a personal experience of 107 cases that I have studied in some detail from 1946 to 1953, and shall refer to some of the facts, figures, and suggestions of some of my colleagues at home.

Incidence of Carcinoma of the Corpus

One of the reasons why we are taking a greater interest in this disease is its apparent increased incidence. I say apparent because it is always extremely difficult to obtain accurate and reliable figures about the incidence of a disease such as this which affects in part elderly patients, many of whom may die of intercurrent disease before they succumb to their carcinoma or having been cured of it. An analysis of female deaths in England and Wales, however, during the five years preceding 1952 shows an incidence of death due to carcinoma of the corpus as half that due to carcinoma of the cervix. All the older writers on this subject speak of carcinoma of the cervix being 4 or 5 times as common as carcinoma of the body.

Apart from a study of mortality records, it is our clinical experience that this disease is now half as common as carcinoma of the cervix; during the interval in which these 107 cases occurred in my own hospital we had 202 cases of carcinoma of the cervix. As far as I am aware there was no deliberate or accidental selection of clinical material, as we are a general hospital serving a wide area of South London which is particularly void of special hospitals which might take special groups of patients. An actual decrease in the incidence of carcinoma of the cervix would of course account for such a relative change in proportion and though there is evidence to suggest that this is in fact taking place I am sure it is not the whole explanation. Nor do I think that increased longevity of the female population accounts for this apparent increase in incidence, because the disease becomes less common in the more

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advanced age groups after 60. Scheffey quotes an incidence of 4 cervix to 1 corpus: but Kottmeier^s gives the figures 2.4 cervix to 1 corpus, and it is now generally accepted in England that a ratio of approximately 2 cervix to 1 corpus expresses the true relative incidence of the two diseases. If carcinoma of the corpus is in fact occurring with increased frequency, then the first essential step in tackling the problem must surely be a closer study of the possible factors underlying its causation.

Evidence for a Constitutional Predisposition

It has been suggested by Way17 that there is evidence that overactivity of the anterior pituitary gland over a very long period of time may be a factor of primary importance and that a hereditary predisposition to such overactivity cannot altogether be ruled out. My own especial interest in the anterior pituitary gland has been largely in relation to the effects of diabetes and the prediabetic state upon pregnancy, because in the so-called prediabetic state there is considerable evidence that overactivity of the gland produces effects upon the fetus many years before it has exercised its effect upon the maternal pancreas by producing clinical diabetes. According to the theory of anterior pituitary overactivity, the effect of this is manifold in its clinical results. On the one hand, by stimulating the ovary or other estrogen-producing gland (e.g., suprarenal) the onset of the menopause is delayed, endometrial hyperplasia and polyp formation are liable to occur, and fibromyomas develop in the uterus; there is a possibility that the growth of feminizing tumors in the ovary is not unrelated. On the other hand, such overactivity has an influence upon carbohydrate metabolism, inducing obesity, decreased This is a very carbohydrate tolerance, and ultimately clinical diabetes. attractive theory which has much to support it, but one wonders whether it is not in point of fact an oversimplification of a problem which has very many facets. I happen to work in a hospital in which there is the largest diabetes clinic in the British Isles, and I have been at a loss to understand why, if these facts about diabetes and carcinoma of the body are indeed true, I have not seen a very large number of patients suffering from these two conditions in association. Scheffey15 gives the incidence of diabetes in cases of carcinoma of the body as 11 per cent, Palmer¹⁴ as 16.9 per cent, and Way¹⁷ as high as 29 per cent. On the other hand, Kimbell⁷ found only 4 diabetic patients among 245 with carcinoma of the corpus, and in my 107 cases there were only 5 diabetic patients. I have looked up the records of the last 100 operations for prolapse during 1954 in the same hospital and find that 6 patients were diabetic; in the previous 94 during 1953 there were 5. Way states that very many of these patients in whom the two diseases were associated developed the diabetes after the cancer. It may be, therefore, that some cases are missed if the diagnosis of the presence or absence of diabetes is determined by a single observation at the time of the initial hysterectomy or radiotherapy. It would not, however, account for the very wide discrepancies which are quoted in the literature (1.2 per cent to 29 per cent). Apart from fully developed clinical diabetes, however, it is claimed by Way that a further 48 per cent had the so-called prediabetic curve. He defines this as one in which there is a raised fasting blood sugar, a high rise, and a curve which at the end of 2 hours was more than 40 per cent above the fasting level. He further states that there was a perfectly normal curve in only 28 per cent of the total carcinoma cases. These figures are very arresting and significant if the interpretation that Way puts upon them is true and if his figures are confirmed by a further and larger series of cases.

During the past 6 months one of the assistants in my department, Dr. J. S. Lewis, has been carrying out glucose tolerance tests on all our cases of carcinoma of the body as they pass through our care in the gynecological wards, but we have also contacted as many as possible of the patients who have been treated in previous years and who are included in the present series. Obviously it was impossible to carry out tests on those patients who had died, but among those who had died were 3 of our 5 diabetic patients. In the remainder followed up, we found three types of curves which are well recognized apart from the frank diabetic ones. The first type of curve I have called abnormal, the second a lag curve, and the third a normal curve (Fig. 1). There is no doubt that the type of curve I have labeled abnormal may have been regarded by the authors I have quoted as prediabetic or even diabetic.

It is on the strength of glucose tolerance curves alone that 19 out of 31 cases were designated diabetic by Way, and 16.9 per cent of 165 cases by Palmer. The exact significance of these abnormal curves in contradistinction to the fully developed diabetic curve is in some doubt, even among the experts. It has long been recognized that this type of abnormal glucose tolerance curve indicating a certain degree of diminished carbohydrate tolerance has been demonstrable in association with obesity, without the slightest evidence of clinical diabetes. Dr. Oakley tells me in a personal communication that this type of abnormal curve is sometimes found in young patients who have been followed for a great many years without the development of clinical diabetes.

In my series I have found 6 abnormal curves apart from the 5 cases of frank diabetes but 5 of the 6 patients were markedly obese and one was 82 years of age. The effect of obesity upon glucose tolerance is as I have said well recognized, but the exact significance of age as such is less certain. Only one of our patients with abnormal curves was under 65 and two were over 80. From such small numbers, however, it would be unjustifiable to draw firm conclusions, suggestive as they are. But it is clearly not justifiable to label every obese person with somewhat impaired glucose tolerance as diabetic, although there might be reason in the argument that they should be regarded as potentially so or prediabetic. In our endeavor to tie up the possible prediabetic factors I obtained the obstetrical histories of those patients on whom we have carried out glucose tolerance tests, and who were parous women. Rather to my surprise there was a history of babies over 10 pounds in only 4 of the patients—3 of them having perfectly normal glucose tolerance curves and one being definitely diabetic. The obstetrical histories of the multiparous patients who had abnormal curves were as follows:

Case 1.—No stillbirth. Birth weights, 6¾ pounds, 7 pounds, 7 pounds. Case 2.—No stillbirth. One baby, birth weight 7 pounds. Case 3.—One child, birth weight 9 pounds, 4 ounces.

Three patients were nulliparas. These figures rather surprised me as Gilbert and Dunlop⁴ have shown that the typical prediabetic obstetrical histories occur chiefly, though not exclusively, in the so-called pituitary type of diabetes associated with obesity. Apart from the 5 diabetic patients, the 6 with abnormal curves, the remainder showed either a perfectly normal curve or else the so-called lag curve (10 cases). The exact significance of the latter is again in some doubt, but it is generally believed to be associated with the absorption of glucose from the gastrointestinal tract rather than with any significant abnormality in carbohydrate metabolism.

My figures are, I am afraid, very incomplete in relation to the incidence of obesity. It is of course essential to relate weight with height in arriving at

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a description of obesity. It is certainly a clinical impression that patients with carcinoma of the corpus are grossly obese women. We can all remember so vividly the heroic surgical struggles associated with hysterectomy in this group of patients and we tend to forget all about the thin patients whose operations were conducted without any struggle with the omental apron and pendulous adipose sporran. But 30 of my cases are definitely listed as obese, and the number is probably a good deal more because I have no information on this particular point from the records of those patients who have died, and who could not therefore be interviewed in the recent follow-up. Way's figure for obesity was 50 per cent, and this is in accord with the figures of other observers.

The relationship of obesity in the elderly with hypertension is also well established, and in my series the high incidence of the latter in association with carcinoma of the body is further emphasized. My information concerning 19 patients is absent or unreliable but, of the remaining 88, blood pressures of more than 170/100 are recorded in no less than 41.

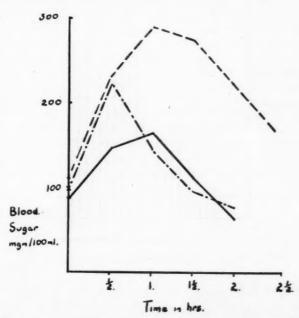


Fig. 1-Normal, lag, and abnormal glucose tolerance curves.

Relation to Time and Type of Menopause

I should now like to consider a problem which is of greater practical importance to us as gynecologists, namely, the relation of this disease to age at the menopause, and its relation to dysfunctional bleeding associated with abnormal endometrial hyperplasia and uterine fibromyomas. These are problems which confront us very frequently in the management of women with irregular uterine hemorrhage at or shortly after the menopause. I have always been brought up to think of carcinoma of the cervix as a disease occurring very much earlier in life than carcinoma of the corpus, and I was taught that the former occurred more commonly in women near to 40, and the latter nearer to 60. Recent figures from many authors seem to indicate, however, that the maximum age incidence of cervical growths is nearer to 50, and that far more cases of corporeal cancer occur under the age of 60 than

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over that age. Figures from my own hospital bear this out. The average age of all patients with corporeal cancer is 58 and, on going through the records of cervical cancer cases, I was rather surprised to find more cases in the 50 to 60 age group than in any other. The age distribution of the 107 corpus cases is as follows:

71 years or over	11 cases
61-71	30 cases
Under 60	66 cases

Twenty-five patients were still menstruating more or less regularly at the time when the cancer was first discovered.

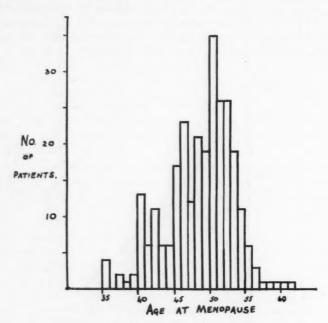


Fig. 2.—Age at the menopause.

It has frequently been stated that patients who develop carcinoma of the body have a later menopause than normal. According to Crossen and Hobbs,³ among patients with fundal carcinoma 60 per cent had a menopause between 50 and 55 compared with 15 per cent of controls, while Way's figures are 54 per cent compared also with a control group of 15 per cent. In estimating the age incidence at the menopause it has always seemed to me open to very serious error if 50 is taken as the dividing line between early and late, and any patient who has a menopause at 50 years is classified as having a late menopause, whereas another ceasing to menstruate at 49 is regarded as normal. It can surely not be not of the slightest significance whether in point of fact the menopause happens at $49\frac{1}{2}$ or $50\frac{1}{2}$ years.

Dr. Lewis has studied the menopausal age incidence in a group of control patients attending the outpatient department. He finds that 50 is, so to speak, the peak age (Fig. 2), with nearly as many patients above that age as below, with an average age of 48.3. According to Larson⁹ the average age at the menopause of a large group with carcinoma of the corpus was 49.1 per cent compared with 48.4 per cent in a control group. It would in fact be a far more significant finding if it could be shown that a considerably larger num-

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far ımber of patients who develop carcinoma of the body had in fact a menopause later than the end of the fifty-second year, compared with a control group of patients. Cosbie and associates² also state that 21 per cent of their patients with carcinoma did have a menopause at 52.

Bearing in mind the fact that there are "lies, damned lies, and statistics," and also that clinical impressions are often wildly erroneous when it comes to an accurate assessment of exact data, nevertheless the figures in my own series seem to bear out a clinical impression I have formed during my years of practicing gynecology. Let me quote a case history which I regard as not by any means unusual in cases of fundal cancer. The patient in question was aged 64. She gave a history of 9 months' irregular bleeding. Prior to that she had been for 3 years with approximately no blood loss at all, but up to the age of 60 menstruation had continued more or less regularly. I stress the words more or less because I find that the accuracy of patients' statements about the regularity or irregularity of their periods at that age are very unreliable and it is often extremely difficult to get a really detailed history. She of course had a carcinoma of the body. To me the significant part of that history is the continued uterine bleeding up to the age of 60.

When I came to look through my own cases I found that 25 patients with fundal cancer were still menstruating more or less regularly at the time when the disease was diagnosed and that in a further 15 the disease was diagnosed within five years of the cessation of menstruation. The average age at the menopause of these 15 patients who developed their disease less than five years after the cessation of periods was 53 years, only one having ceased to menstruate before 50. Ten of the 25 patients still menstruating at the time of diagnosis of their disease were over 52. If one excludes all these cases there were 61 left who developed fundal cancer more than 5 years after the menopause. The average age at the menopause in this group was 48.3 years which is perfectly normal (15 at 50, 29 below 50, 17 above). The conclusions I feel justified in drawing from these figures and observations are these:

A. It can matter little if anything whether a woman has a menopause at 49 or 51.

B. If a patient continues to have regular periods till she is 52 or 53 and then stops completely she is no more likely to develop carcinoma of the fundus when she is 75 or 80, if she lives that long, than if she had ceased to menstruate at 47 or 48.

C. The continuance of irregular menstrual bleeding beyond 53 or 54 should make one very much aware of the possibility of carcinoma being actually present or likely to develop in the not very distant future.

This brings us to a further point for consideration. Is it in fact the delayed menopause or is it the dysfunctional bleeding associated with endometrial hyperplasia that is the important factor? My feeling is that it is the endometrial hyperplasia that is the significant feature, especially when it is associated with a delayed menopause. Endometrial hyperplasia is due to the prolonged unopposed action of estrogens upon the endometrium. With the approach of the menopause there occurs presumably a steadily decreasing influence of progesterone, so that varying degrees of progesterone deficiency can be observed in the endometrium up to complete lack of any influence. The estrogen influence may be exaggerated by their clinical administration, or by their clinical production in the body, if not from the ovary itself, from other endocrine organs such as the suprarenals or from an estrogen-producing ovarian tumor. Both the administration of estrogens therapeutically and the development of granulosa-celled tumors in the body are known to be causes of endometrial hyperplasia: but do they cause cancer? Evidence from the literature concerning the association of endometrial hyperplasia and malignancy is very conflicting. Larson⁹ produces evidence against the association of the two conditions and points out that endometrial cancer can occur in castrated women. But endometrial hyperplasia (nonmalignant) can also occur in postmenopausal patients who have not received any estrogens therapeutically. I recently saw such a patient, aged 78, who had a typical metro-

pathic endometrial hyperplasia (Fig. 3).

Novak¹² points out that carcinoma of the fundus occurs in association with granulosa-celled tumors only in elderly patients. In younger women such tumors induce endometrial hyperplasia but malignancy is very rare indeed. On the other hand, Linburg¹⁰ finds 50 per cent of 363 cases of carcinoma of the corpus associated with endometrial hyperplasia. Te Linde and associates¹⁶ suggest that many cases of hyperplasia, proliferation, and atypical adenomatosis are in fact cancer very much as carcinoma in situ in the cervix is regarded by most pathologists as cancer. Endometrial hyperplasia and malignancy do occur in the same uterus and such an example is seen in Fig. 4. In my own series, however, we have had only 2 cases of granulosa-celled tumors in association with malignancy of the endometrium, which is a lower incidence than

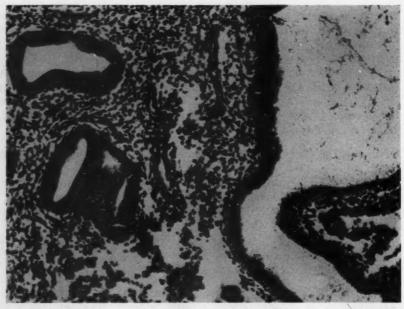


Fig. 3.—Metropathic endometrium from patient aged 78 years (no granulosa-celled tumors nor estrogen administration).

most authors quote. Nevertheless, there must be other factors than the action of the estrogens. When these tumors occur in younger women they may cause a very severe degree of endometrial hyperplasia but not malignancy.

The same applies to the occurrence of endometrial polyps and the growth of fibroids. Accurate figures are difficult to obtain about the incidence of polyps in association with carcinoma of the corpus, because they are often not recorded or may be entirely missed, but all authors quote a high incidence of fibroids in association with this disease. Way quotes a 34 per cent incidence, and my own figures are very similar—33 out of 107. But here again generalization from such observations can be very misleading, and it is very difficult to

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do wn ssohan rationalize any association in a woman of 75 years, between a small localized carcinoma of the fundus and one or two small subserous fibroids she may happen to have in the uterus. On the other hand, a case history such as this is, I think, very arresting. Fig. 5 shows the uterus removed from a patient aged 49. She gave a history of irregular bleeding for nine months, the periods having been heavy but fairly regular before that. A large mass of fibroids was palpable in the lower abdomen rising up to the level of the The endometrium as you can see is grossly hyperplastic and umbilieus. polypoid. It is a typical metropathia hemorrhagica in part; adenocarcinoma in another place (Fig. 6). One could multiply this type of case several times in any series of cases of carcinoma of the body. It cannot be merely that in this patient there was an abnormal production of estrogens; there must be some local tissue sensitivity affecting the whole organ, endometrium as well as myometrium, and it is the local tissue sensitivity which is the really significant thing.

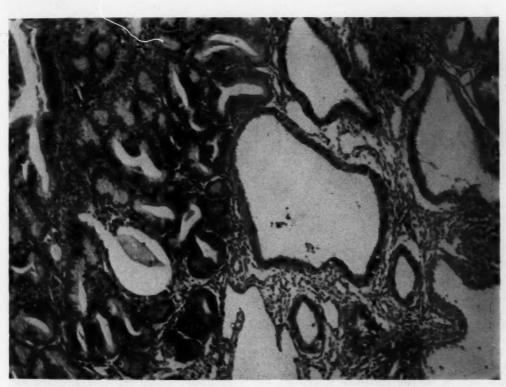


Fig. 4.-Metropathia coincident with adenocarcinoma.

I think personally that there are real practical problems arising from these observations. How far are we to go by carrying out hysterectomy as a prophylactic against the development of carcinoma of the body? Are we to take note of every patient who continues to menstruate after the age of 50; are we to advise hysterectomy for a few symptomless fibroids in a patient whose menstrual periods have ceased or are perfectly normal; are we to advise radical treatment in every case of dysfunctional bleeding about the time of the menopause? Does the fact that the patient is fat or thin influence us at all or that her carbohydrate metabolism may be suspect? If we attempt to epitomize the little we know about the etiology of this disease, the evidence

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points to the fact that the unopposed action of estrogens over a relatively long period of time predisposes to malignant endometrial hyperplasia only under certain circumstances, the most important of which is that the patient is menopausal in age or older.

Sometimes the whole endometrial surface becomes malignant simultaneously; in other cases there may be large portions of the endometrium quite innocent; yet again in another common group we find most of the endometrium completely atrophic and only a small localized region where malignant hyperplasia has occurred. Only if the impact of such abnormal estrogenic influence has fallen before the menopause will fibroids develop in the myometrium; but we have no real idea why this should be so, for I know of no evidence to suggest that a woman who develops a granulosa-celled

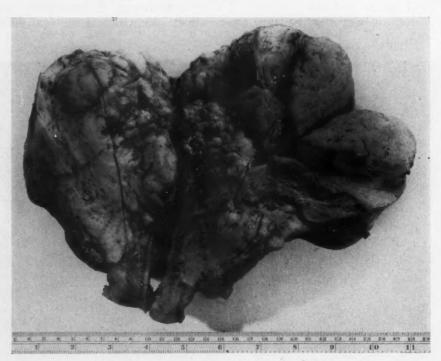


Fig. 5.—Uterus showing fibromyoma, endometrial hyperplasia, and carcinoma of the endometrium.

tumor at the age of 70 would be likely to develop any new fibroid growth in the uterus if the fibroids were not there already. And why, if fibroids are present in the uterus of a woman of 70 who then develops a carcinoma of the endometrium, do the fibroids not increase in size, and show evidence of active growth too? The more we think of these problems the more we appreciate the appalling gaps in our knowledge and understanding of the processes involved in neoplasia.

Special Types of Cases

Nevertheless I think that certain pertinent conclusions can be drawn from the facts we do know. These together with clinical observation lead me to divide the carcinoma of the body cases into two more or less distinct groups. The first group represents about 40 per cent of my cases. They are the patients who develop carcinoma of the endometrium round about the age of

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the menopause, a few years before or more often a few years after the age of 50. Their menstrual history is usually that of irregular periods with bouts of excessive or prolonged bleeding, associated with endometrial hyperplasia, and often fibromyomas or both. It is in this group that the delayed menopause is very much in evidence and often these patients bleed excessively and irregularly up to the age of 55 or more. In some a short period of amenor-rhea may occur before the carcinoma becomes manifest clinically or histologically. Very often in this group of cases if fibroids have not developed in the uterus there occurs a great deal of diffuse myometrial hyperplasia.

I well remember one patient in whom the uterus was easily palpable in the abdomen and on removal it was about the size of a 14 weeks' pregnancy. There were no fibroids and the endometrial carcinoma was confined to the endometrium and there was no infiltration of the myometrium by growth.

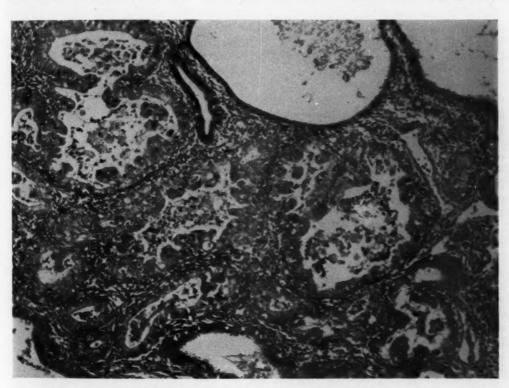


Fig. 6.-Metropathia associated with adenocarcinoma.

This group of patients is a very important one from the point of view of diagnosis. Unless the association of endometrial carcinoma and myometrial hyperplasia or fibromyomas is constantly kept in mind an incomplete operation may be undertaken for the cure of malignant disease. It at once raises the question whether in fact a diagnostic curettage should be carried out before hysterectomy in all cases of fibroids or enlarged uterus after the age of 40. Some authorities have gone so far as to suggest that this should in fact be done, however large the mass of fibroids.

I do not wish to digress into the use of the vaginal smears in the diagnosis of fundal carcinoma but most authorities agree that the smear is less accurate in the diagnosis of endometrial than of cervical cancer and that a diagnostic curettage is necessary in all cases by way of confirmation. The

practical difficulty of doing a curettage on a uterus grossly distorted and enlarged by multiple fibroids is very real, with a high risk that a small or early carcinoma might be missed. It is my own practice to do a preliminary curettage in all cases where there is marked irregularity of uterine bleeding or intermenstrual bleeding, even though the uterus is full of fibroids which at first sight seem an adequate cause for the patient's symptoms.

The second group of fundal carcinoma cases are those in which the disease develops only after a prolonged period of amenorrhea following the menopause. This may be twenty or thirty years after the menopause. tumors tend to be more localized in these cases, the remainder of the endometrial surface being the normal postmenopausal atrophic one. represents about 60 per cent of my cases and is the textbook type of case presenting with postmenopausal bleeding. In my cases the menopausal age was perfectly normal in this group and it is indeed very difficult to credit that a menopause delayed for one or two years beyond the average should be of any significance in the development of a localized tumor in the endometrium some twenty or thirty years later. Again in this group one often finds small atrophic fibroids, but one wonders whether there is any connection between the two. A certain percentage of these women are obese and if they are obese they do manifest a disordered carbohydrate metabolism with diminished glucose tolerance and an abnormal glucose tolerance curve. It is my own feeling that the disordered glucose tolerance in this group of patients is associated more with the obesity than with the endometrial carcinoma, and such figures as I am able to produce at present seem to bear this out. We know that there are both constitutional and hereditary factors at work in the production of obesity and decreased carbohydrate tolerance, and it may be that as Way suggests there are similar factors influencing the development of endometrial cancer. But I think it remains as yet unproved, attractive though the theory may be.

Before I leave the subject of etiology and discuss very briefly treatment, I should like to mention two unusual types of endometrial malignant tumor that are sometimes seen, first, the so-called adenoacanthoma, and, second, the carcinosarcoma. The first is not so very rare, there being 5 cases in my series of 107. Novak states that in his experience this histological change occurs chiefly in adenocarcinomas of lesser degrees of malignancy, which carry a relatively better prognosis (Fig. 7). All my 5 cases fell into that category. All the patients were very elderly, developing the disease 10 or more years after the menopause. Four of the patients are alive and well, one having died of pulmonary embolism following operation. My one patient with carcinosarcoma was aged 34 (Fig. 8).

Points on the Therapy of Carcinoma of the Corpus

Now I should like to discuss briefly a few points about the treatment of this disease. Following diagnosis we used to be content with a total hysterectomy, after suturing or plugging the cervical canal, together with removal of both tubes and ovaries, as a five-year survival rate of approximately 60 per cent was looked upon as a very favorable state of affairs in the management of malignant disease. Within recent years, however, we have all become more and more aware of the inadequacy of such an operation. I think the reason for our changing attitude to the management of this disease is due to the following factors:

1. Following the relatively conservative operation of total hysterectomy and bilateral salpingo-oophorectomy there is a high incidence of recurrence in the vault, which is usually early, within a year of operation.

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Fig. 7.

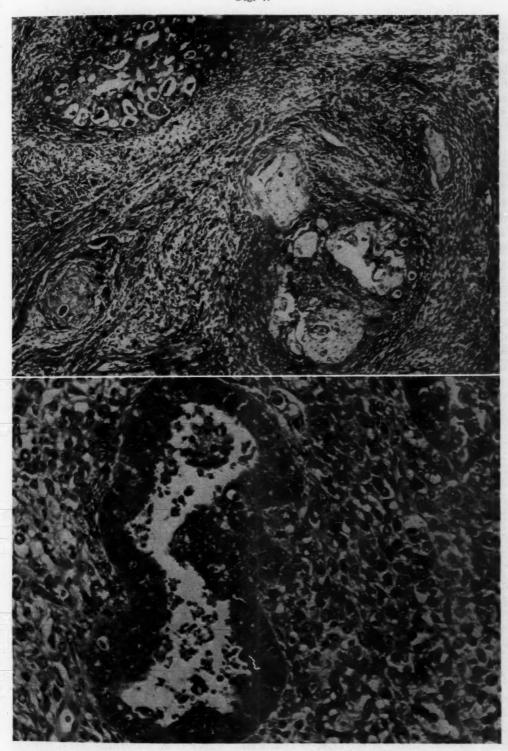


Fig. 8.

No. 7.—Adenoacanthoma. No. 8.—Carcinosarcoma.

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2. The results of radium therapy in certain centers, particularly the Radiumhemmet and the Marie Curie in Europe, made us realize that many of these tumors must be relatively radiosensitive.

3. The increasing awareness that in cases where the growth involves the lower third of the cavity and/or the cervix, intrapelvic lymph nodes may well be involved has led to the realization that in many cases a more radical surgical operation is necessary. And so we have been evolving in the past ten years a new technique, which combines radiotherapy before or after operation with more radical surgery.

I do not think anyone has yet enough figures to give final results of this more radical operative technique but at a recent meeting of the Royal Society of Medicine, Winterton¹s spoke of a 76 per cent five-year survival following a Wertheim-type operation, and Rickford's (1954) figure was very similar—74.2 per cent. Some of Rickford's patients received pre- or postoperative irradiation.

It is nearly 10 years ago that I first started employing preoperative radium in some of these cases, but only more recently have I employed it as a strict routine. I use an intracavitary dose, with vaginal vault applicators according to the Manchester technique, and give a dose of 3,500 r. I think there are several virtues in the preoperative use of radium. In the first place, irradiation can be applied at the time when the first curettage is done. If the growth is small it may almost disappear by the time the hysterectomy is undertaken; if it is more extensive it has shrunk a good deal and the superficial cancer cells have been destroyed, so that implantation growth is less likely to occur. The presence of secondary deposits in the vault at the time of the initial operation has been demonstrated in some cases, and therefore it seems rational to irradiate the vaginal vault as well as the cavity of the uterus. Whether these vault recurrences are due to implantation during the course of operation or to lymphatic or venous spread which may precede operation has not yet been proved, but it seems possible that both may occur.

My own figures are not large enough to give you any final results of preoperative radium therapy combined with surgery. I can say that in the last seven or eight years I have seen no single case of vault recurrence, if preoperative radium has been used, and 5 cases in which, for one reason or another preoperative radium was not available or not used, in which early vault recurrence developed. All but a few of the patients who received preoperative radium had a simple total hysterectomy after suture and plugging of the cervix, and not a removal of the vaginal vault.

Having recently seen a vaginal recurrence 14 years after an initial hysterectomy for carcinoma of the body, I realize that one must be a veritable graybeard before one's personal experience is long enough to follow all one's cases to their ultimate end, and a final-and-forever cure for any form of cancer seems a long way off. Nevertheless, my own personal experience with preoperative radium is so far entirely favorable and the only disadvantage that I know is that one may not always have the radium available at the time one may unexpectedly find a carcinoma on curettage. I think in such cases one should proceed to surgical removal and follow this with vaginal radium postoperatively.

In spite of my good results so far using preoperative radium, in regard to secondary recurrences in the vault, I am not entirely satisfied that a simple total hysterectomy is all that is required. I now aim to isolate both ureters as we used to in the older types of Bonney-Wertheim hysterectomy for carcinoma of the cervix, and remove a cuff of vaginal vault. Nevertheless, I hesi-

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tate to do this as a routine. Many of these patients are very elderly, and a large number obese, some being very obese indeed, so that it may on occasions be very little short of impossible adequately to carry out such a radical operation without unjustifiably adding greatly to the primary risk. Surgery has today become so relatively safe that we sometimes tend to lose our surgical judgment in the pursuit of a rigid routine. If vault recurrence occurs in spite of preoperative radium, suture of the cervix, and removal of the vaginal vault, then surely we cannot blame ourselves for the inadequacy of our surgical endeavors.

The next problem for consideration is whether we are to be content with bilateral salpingo-oophorectomy and removal of a cuff of vaginal vault. The frequency with which cancer cells may pass down the Fallopian tubes as well as by lymphatics, recurring along the top of the broad ligaments, has been demonstrated by Haines⁵ and other pathologists. We all now make a point of clamping or ligaturing the fimbrial ends of the Fallopian tubes to prevent possible spill of cancer cells which may take place even in spite of preoperative irradiation. But perhaps of greater importance is the question of whether an intrapelvic lymph node dissection should be carried out as in the radical operation for carcinoma of the cervix. If the growth involves the lower part of the cavity or the cervix then there will certainly be a percentage of our cases with intrapelvic lymph node involvement and the logical step is a lymphadenectomy as part of the radical operation. Attempts have been made by many authors to determine the extent and distribution of the growth preoperatively by fractional curettage, and so to predetermine in which cases an intrapelvic lymphadenectomy should be employed.

Those surgeons who have so far carried out lymphadenectomy in their cases give figures for involvement that are not capable of real assessment as yet. Javert⁶ quotes 14 in 50 cases (28 per cent); Meigs¹¹ 23 per cent; Townsend in a personal communication about 20 per cent. The total number of cases is small and to some extent selected, whereas Winterton¹⁸ found only 5 to 6 per cent in a small series of unselected cases. But these figures are very surprisingly high.

Should we therefore do routine intrapelvic lymphadenectomy or should we attempt to select cases suitable for this more radical procedure? I confess that my mind is not quite clear on this point. In most cases where the lower third of the cavity is extensively involved, and even more so in those cases involving the cervix, the growth is likely to be so advanced in the fundus that lymphatic spread has probably taken place along the ovarian lymphatics to the para-aortic nodes. In my experience, a common site for recurrence in advanced cases after operation is above the pelvic brim. In such cases, therefore, even though the intrapelvic glands are involved, it is most unlikely that their removal will affect the ultimate issue. The chances of intrapelvic lymph node involvement in earlier cases not invading the myometrium and confined to the upper two-thirds of the cavity are so remote that it is questionable if the added operative risk is justified in a fragile, obese, and sometimes very elderly patient.

My experience with vaginal hysterectomy so stoutly upheld by Bastiaanse¹ is very limited. I recently found it had a place in an elderly patient of 84, grossly fat with an enormous ventral hernia and a very bad chest. I think an abdominal operation would have killed her but fortunately her growth was early and she stood up to a vaginal hysterectomy of the modified Schauta type surprisingly well. I believe it has a place but a very limited one.

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Conclusions

In this talk I have gone over a lot of ground that you probably all know very well. I have given you a great many of other people's ideas and a few of my own. Problems both of etiology and of treatment require a good deal more time and research before some of the suggested factors in etiology or methods of treatment can be discarded or accepted. The subject is one full of interest and it is good to know that we have all been shaken out of a somewhat complacent and self-satisfied attitude toward this disease. There are many facts that are food for thought, and for further enquiry, but it is clear that the last word has not yet been spoken concerning the cause, the prophylaxis, or the treatment of this disease.

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CONDITIONING FOR CHILDBIRTH*

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CARL TUPPER, M.D., F.I.C.S., HALIFAX, NOVA SCOTIA

(From the Department of Obstetrics and Gynaecology, Dalhousie University)

THIS paper is based on an experience with over 1,200 women who have undertaken what is commonly called natural childbirth, and covers the years 1950-1954, inclusive. When, having read Grantly Dick Read's books on the subject, we undertook this experiment, we were highly skeptical of the claims made for it. After four years' experience we are still skeptical of some of the claims made for it, but—those of us who have given it a fair trial—are now convinced that it can become a very valuable factor in solving the problems of childbirth.

What are the three great problems that beset us as obstetricians today? Could we not agree that the following are among the most pressing?

- 1. The relief of pain during labor, for which, either with sedatives or anesthetics, we have no fully safe, satisfactory, and simple method.
- 2. Our present still high neonatal mortality and morbidity, some of which result from asphyxia due to overdoping of the mother during labor.
- 3. Our situation as a continent of small families in a world of large families, due to the civilized woman's inability to obtain the satisfaction and prestige from having a baby that the process should entail.

I do not think it is necessary for me to argue about the validity of problems 1 and 2. The very multiplicity of methods in use, and the almost frantic search our specialty keeps making for new ones are in themselves ample evidence of our dissatisfaction with the ways in which we try to relieve pain during labor. Nor can anyone argue that the number of newborn babies who die of asphyxia because they are doped is not still too high. But I would like to say a further word about problem 3.

Why does modern woman not derive the satisfaction from having a baby that the importance of what she is doing entitles her to? For one thing, society gives her little if any prestige in the matter. It is a man's world, and if a woman wants to gain the plaudits her husband gains, she must take up one of his pursuits to do so—write a book or act in a movie or run a business. Nor have we as obstetricians done anything to alter this state of affairs. Quite the reverse. In order to make childbirth as safe and painless as possible for her, we have practically taken over the procedure from her. We direct almost every step she takes during the pregnancy, labor occurs in our hospital

^{*}Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynae-cologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario.

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rather than in her home, and we so dominate the final stages of delivery that she is usually unconscious when the baby is born—in a very high percentage of cases aided by our so-called "prophylactic" forceps.

Furthermore, our maternity hospitals, or departments, are designed not so much to deal with normal labor but with the emergencies of labor. They are just like all other hospitals. When they were first designed, only women with obstetrical emergencies were admitted to them, the normal patient being delivered in her home. Today, practically every woman having a baby is delivered in a hospital. But our maternity hospitals are neither designed for, nor are they psychologically suited to, this purpose. The prevailing atmosphere is that of sickness and pain, of dealing with a pathological rather than a physiological process.

It is the impression in Halifax, of those of us conscientiously practicing natural childbirth, that it is a distinct help—even with the limited amount of conditioning we attempt—in dealing with the three problems just mentioned.

Relief of Pain

Unfortunately, natural childbirth was hailed at first as a method of painless labor. Even Grantly Dick Read, its popularizer, stressed it as such. The impression was conveyed that there was something inherent in the relaxing exercises that removed pain. Although Read did explain that it was the relief from fear and tension that produced the real benefit, the idea got abroad that natural childbirth meant painless childbirth.

This was the impression we ourselves had, but we soon realized that two things were happening to our patients: (1) they were certainly feeling pain, but (2) they were nevertheless enthusiastic about the regime.

Very shortly after beginning our experiment we realized that we must, except in a small percentage of cases, accept pain as a concomitant of this method. But why, although they did suffer pain, were the women so enthusiastic about it? We began to watch the woman in labor more closely, and it soon became apparent to us that—as Read had pointed out—fear was the major problem, fear acting in a vicious circle. The woman felt pain during a contraction so became afraid that she would not be able to bear the pain of the subsequent contractions. This fear carried over into the interval between the contractions as a sort of panic. The panic so heightened her sensibilities, that she actually felt the pain of the next contraction more acutely than she would have. So there was more panic carried over into the next interval, more pain with the contraction following that interval, and finally a complete breakdown of morale, with screaming and terror during the contraction, and abject loss of emotional control in the interval.

This phenomenon was seen particularly in two groups of women: (1) the badly disciplined and emotionally unstable type, and (2) the woman who, despite having faced the first part of labor with fortitude, became exhausted from effort and loss of sleep, eventually losing control. Even women who train for natural childbirth tend to lose control when labor has lasted longer than eighteen hours. It seems not unlikely that in this second category of women, after a long time in what seems to them fruitless labor, fear enters their minds that they may not be able to push the baby out, and this fear is added to the fatigue and loss of sleep as factors bringing about a breakdown in morale.

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It seemed to us that the major effect of our natural childbirth training was on the interval, rather than directly on the uterine contraction. If, immediately following the contraction, the woman relaxed physically and mentally, and remained free from anxiety and tension, she did not appear to mind the next contraction. In effect, by relaxing during the interval, she got her emotional cylinders recharged against the next contraction. In some of our cases she actually did not seem to feel as much pain with her contractions as we would normally have expected. This was a minority, approximately one fifth. In the vast majority of successful cases, the woman appeared to feel the pain of the contraction but, having been braced against it by the relaxation and lack of tension during the interval, she did not mind it. There is a difference between feeling and minding pain.

We believe that this relaxation and freedom from tension in the interval are most important, and we doubt very much if any woman can relax physically to any great extent while the uterus is contracting. Certainly, a woman bearing down in the second stage of labor cannot be said to be relaxed physically. We have on many occasions been called to a patient who has lost control toward the end of labor. She was crying out with her contractions, thrashing around on the table in the intervals, thoroughly out of control. But after talking to her for a few minutes, sitting with her through a couple of contractions, reassuring her about the progress of labor, we have been amazed to see this woman regain control, become relaxed and free of tension during the intervals, and bear down with her contractions with little evidence of the pain that had previously seemed so severe. It is therefore our feeling that if we can keep our women free of fear and panic during the intervals, the contractions will look after themselves. But we do not pretend either to ourselves or to our patients that the contractions are painless.

To what extent do our patients appear to get relief from pain or to be able to bear pain better—in other words what is their total performance? The results obtained are very much the same as those of Thoms¹ and others. Table I illustrates our method of classifying these results. Let me say that in all these cases the perineum was infiltrated with local anesthetic late in the second stage of labor when it was bulging before the presenting part.

TABLE I. TOTAL PERFORMANCE

SEDATIVE	ANESTHESIA	LABOR TYPE	WILL REPEAT
None	Local	Spontaneous	Yes
One only	Local	Spontaneous	Yes
1 or 2	Local and Trilene	Spontaneous	Yes
1 or more	General or spinal	Mostly forceps	Yes
	None One only 1 or 2	None Local One only Local 1 or 2 Local and Trilene	None Local Spontaneous One only Local Spontaneous 1 or 2 Local and Trilene Spontaneous

The excellent cases were those requiring no sedative or anesthesia; were spontaneous deliveries; the patients were enthusiastic about the procedure and would have their babies this way again, and in the opinion of the Case Room Supervisor and Natural Childbirth Specialist were superior cases. Those scoring very good were much the same but they asked for and were given one sedative. Those considered good required a bit more sedation and requested whiffs of Trilene. Many patients, for various reasons, were given general anesthesia; some requested it themselves, while more often the doctor requested it. These, plus any case requiring forceps, were classed as "helped." I might say that many of these did well and felt the method was good and all wanted to have their babies this way again. The failures apparently were not benefited and would not repeat.

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Table II shows the results of the total performance. We see that 70 per cent of the primiparas and 75 per cent of the multiparas had spontaneous deliveries with no general anesthesia.

TABLE II. PERFORMANCE FIGURES

PERFORMANCE	PRIMIPARAS (%)	MULTIPARAS
Excellent	19.7	46.5
Very good	22.6	10.7
Good	27.7	17.8
Helped	22.0	17.8
Failures	8.0	7.2

One fifth of our primiparas got through labor without a sedative during the first stage and with nothing but local anesthesia in the perineum and episiotomy in the second stage. Another fifth had to have a sedative, Demerol, 1 mg., or heroin, ½ grain, and thereafter got through with only the local anesthetic in the perineum. About one fourth had a sedative and were given a whiff of Trilene when the head was fully distending the perineum, but seldom to an amount that affects the woman during the interval more than a stiff drink of whisky would. The less satisfactory cases require more sedative and more terminal Trilene, or a deeper general anesthetic for the terminal contractions (Table II).

Let me repeat that it is our distinct impression that while the conditioning we give our women may not actually lessen pain it certainly makes it more bearable.

Effect on the Baby

How does natural childbirth affect the baby? Prior to its introduction in our department, resuscitation was a common problem, and we were constantly suffering anxiety over babies who would not respond because they were doped. Now this anxiety has all but disappeared and it is very gratifying to have baby after baby cry immediately and lustily.

Table III shows a brief study of 100 babies delivered under the natural childbirth regime as compared to 100 babies delivered in the routine fashion. These results were recorded through the observation of the obstetrical resident, the pediatrician, and the nursery supervisor. These babies were closely watched and compared, so that an unbiased opinion could be obtained. The staff of the nursery were not aware of whether the baby was a natural childbirth infant or a control.

TABLE III. NATURAL CHILDBIRTH BABIES COMPARED TO CONTROL BABIES

	NATURAL CHILDBIRTH SERIES	CONTROL SERIES
Average time to breathe	5-10 seconds	20 seconds
Average time to cry	10-15 seconds	50 seconds
Happiness less than good	9	13
Irritability	8	14
Relaxation less than good	7	11
Need for resuscitation	3	15
		(6 had to be intubate

Under "need for resuscitation" we included all babies who required more than one minute to breathe. Some of these required no help, which was the

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case of the 3 natural childbirth babies, other than a little oxygen. In 6 of the 15 control babies, however, a tube had to be passed into the larynx before breathing was established.

We conclude that natural childbirth babies are better babies. They breathe and cry more spontaneously, are less irritable, are happier, and cer-

tainly require less resuscitation.

We have talked this matter over with our pediatricians and the supervisors of our nursery, and they are very decidedly of the opinion that the natural childbirth baby is a less morbid baby.

Forceps.—Furthermore, natural childbirth has cut down the number of so-called prophylactic forceps applications, with the result that fewer babies are as tense and difficult as any type of forceps baby tends to be. In our hospital over the past three years forceps, mostly so-called prophylactic, have been applied on the average in approximately 30 per cent of deliveries in private cases. Our natural childbirth rate is 18 per cent of private cases studied, about half that of the over-all figure for the hospital.

I would like to say that the forceps application rate in our natural childbirth cases is not as high among those of us who practice it consistently, that is, who have patience enough to allow the woman a reasonable time in which to

push the baby out, the rate here being 12 per cent.

Breast Feeding.—The woman undertaking this training seems to have a higher sense of duty toward her baby, with the result that a higher percentage

of them are prepared to nurse.

In a control series, 50 per cent of the mothers nurse, as compared with 65 per cent of primiparas and 64 per cent of multiparas in the natural childbirth series. This, in the days of the declining tendency toward breast nursing is an important factor, although we cannot really be proud of a figure as low as 65 per cent.

Satisfaction of the Woman

Of the women who have undertaken natural childbirth, not only those doing it for the first time, but those who have had previous deliveries under other regimes, approximately 90 per cent are enthusiastic about it; 87.5 per cent of primiparas and 85.7 per cent of multiparas state that they will repeat it. It seems to have constituted for them a more satisfying experience.

In the past, let me repeat, in our attempts as a profession to make child-birth not only safer but as painless as possible, we have in effect practically taken over the procedure from the woman. Labor occurs in our hospital and we do so dominate the final steps of delivery with our methods that she usually is unconscious when the baby is actually born. When, sometime later, she is presented with this baby, she has to take our word for it that it is her baby. Considering the fact that, for the vast majority of married women, having a baby is the most important thing that they do—the one thing they can do that we men cannot do—our domination of their pregnancy and delivery thus robs them of a considerable amount of the psychological satisfaction they might derive from the process. More and more we, and less and less they, are having the baby.

Natural childbirth seems to reverse this situation, so that the women, despite the fact that we still play an important part, feel that they are having the baby, and that we are simply auxiliaries to the fact. Our training during pregnancy and their own conduct during labor bring this out. When the baby is born, and while it is still attached to them by the cord, it is held up so that they can see it. They know it is their baby, and they know that they pushed it into the world more or less unaided. This seems to give them a

very great psychological lift. At first we were highly skeptical of this reaction, but it occurs so constantly that we now realize that it probably constitutes the great satisfaction of natural childbirh.

Method of Conditioning

Our methods of conditioning are very simple. On her first visit to us the woman is given a mimeographed letter which states in easily understood language and with diagrams what is going on inside her during pregnancy and what will go on inside her during labor. She is told what will be done for her during pregnancy and labor and why. She is also given a pamphlet describing what natural childbirth is and what it is likely to do for her, and we have taken great pains to make no false claims. She is given her choice as to whether she will try it or not, but it is made clear to her that she is committed only to try it and that, if she finds she cannot go through with it, she will be given sedatives and anesthetics at her request. The pamphlet contains three simple breathing exercises which she is exhorted to do daily until they become automatic.

The Breathing Exercises .-

In the beginning we used some of the many so-called relaxing exercises described in the various books written on the subject, but we have found that the following three simple exercises are just as effective and have the added advantage that they seem to the woman more completely integrated with her labor problem:

1. Lying in the position shown in Fig. 1, breathe gently in and out. As you breathe in let your stomach rise; as you breathe out let it fall. Do this several times. Now draw in your breath slowly; try to take half a minute to do this if you can. Let it out slowly, trying to take half a minute. Repeat this slow-breathing exercise several times. This is the way you are to breathe while your womb is contracting during the first stage of labor, while the mouth of the womb is slowly opening.

The first exercise is the one she uses during her contractions in the first

stage of labor.

2. Breathe gently in and out, letting your breastbone rise and fall with each breath (Fig. 2). Now open your mouth and breathe quickly in and out, panting like a dog. This is the way we may ask you to breathe if you are having trouble in the last half hour of the first stage of labor, when the mouth of the womb is almost fully open.

The second exercise is a sort of emergency exercise that she uses during

any contraction that is unusually painful.

3. Bend your knees so that your feet are flat on the bed. Now draw in a quick deep breath and bear down as though trying to move your bowels. Bear down as hard as you can. Repeat this several times. It is a very important exercise. We will ask you to do this each time the womb contracts during the second stage of labor, when the baby is being pushed down the front passage.

The third exercise is simply a training in the best method of utilizing the contractions of the second stage, something that a surprisingly large number

of women do not seem able to do spontaneously.

We try to teach the patient to remain relaxed in the first stage not only during the contractions but in the interval between them. This rests her and keeps her strength up. During the second stage, when she is bearing down she cannot relax with the contractions, but we do our best to have her relax as fully as she can in the intervals.

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The Hospital.—Around the fifth month we send her to a clinic where two nurses trained especially for the purpose put her through her exercises, to make sure she is doing them properly and show her on life-sized models what goes on during labor.

Patients get this training in small groups and are encouraged to turn the occasion into a forum for the discussion of their difficulties and problems. They attend two such sessions. On the second of these they are taken to the maternity hospital and introduced to everyone they are likely to meet there, and shown the delivery room so that they will not come to the hospital as strangers. In the hospital itself, they are not taken immediately to the delivery room, but spend all the first stage of labor and as much of the second as possible in a section adjoining it, so that they are out of the atmosphere of blood and turmoil so frequently unavoidable in the actual delivery room, as long as possible.

As nearly as possible, we try to have someone with the patient during her entire labor, whether it be friend, nurse, husband, or intern, and we feel this is very important. We have instructed our hospital personnel especially in the handling of these women, the emphasis being always on the prevention of fear, anxiety, and tension.



Fig. 1 Fig.2

One thing we would stress and that is that it is not enough for the individual doctor to practice this procedure on his own. While he can do much as an individual to build up the woman's morale and train her to meet this greatest test of her fortitude, the hospital in which the baby is to be born must also play its part. Maternity hospitals, or the maternity departments of general hospitals, tend to imitate the procedure of hospitals in general. It is our belief that the maternity hospital or department should present a different face to these women than any other type of hospital. It does not matter much to the woman having her gall bladder removed if she did not like the nurses or the care she got, or the way she was handled—she has only one gall bladder to lose. But if we are to reproduce our population from our own stock, every woman having babies must have three, and it is therefore racially important that her experience in her maternity hospital be a satisfactory one.

We have found the hospital the most difficult part of our natural childbirth technique. To make sure that nothing happens to the woman in the hospital to increase her fears or anxieties, to have someone with her or at her call throughout the entire labor, to arrange the hospital physically so that she does not have to be in close proximity to the delivery rooms until she needs to go there, to protect her from the behavior of the less disciplined woman who is making outcry, to instill into the hospital personnel the philosophy necessary, all these things are not easy of achievement and take a great deal of time and attention. Nevertheless, they are vitally important to the success of natural childbirth.

The Doctor.—One of our main sources of failure has been the impatient doctor. All our natural childbirth women are trained by two nurses during

pregnancy. They are prepared to go through labor according to the procedure laid down. But their doctor, who may give only lip service to natural child-birth and has agreed to it only because it was asked for, arrives for the delivery and, finding the head a little slow in dilating the perineum, gives the woman a general anesthetic and applies low forceps. This sort of medical impatience is responsible for many of the failures in our statistics—it was also responsible for a good deal of disappointment on the part of some of the women who felt cheated.

Comment

It is our impression that conditioning a woman for childbirth does very much the same for her that military training does for a young soldier who must face the rigors of battle. No young man wants to die or to suffer the pain of wounds. But with military training he becomes so conditioned that he is able to face death and pain with fortitude, and to come through the experience with a sense of having proved his manhood. Our only apology for the training we are giving our women is that it does not go far enough and is not comprehensive enough. If we can get the results we have obtained with the slight amount of preparation we are giving these women now, what might we not achieve if we could persuade women to prepare for pregnancy and labor with the care that we train our young men for war, or even with the care that a prize fighter gives to preparing for a fight. If, in addition to this, we could persuade ourselves as obstetricians to play a less active part in delivery, and whenever possible allow the woman to feel that she is accomplishing it herself, not only would very much better results be obtained but women would look on having a baby as a very much more satisfactory experience than it now is.

Summary

To sum up, we believe that if natural childbirth or, as we prefer to call it, conditioning for labor, is used not so much for its relief from pain as for its psychological effect on the woman, permitting her to derive a greater satisfaction from having a baby, it is a most valuable addition to our obstetrical armamentarium. Furthermore, it is our opinion that any undertaking which makes having a baby a more attractive and satisfactory process is worthy of our consideration as a profession working on a continent where small families are the rule.

I wish to acknowledge with thanks the help of my Professor, Dr. H. B. Atlee, in preparing this paper.

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THE SAFE AND SIMPLE DELIVERY OF PERSISTENT POSTERIOR AND TRANSVERSE POSITIONS*

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IT IS proposed to describe a maneuver for the safe and simple delivery of fetuses arrested in the oblique occiput posterior, or transverse, positions—safe for both mother and child, and simple, inasmuch as a perfect cephalic application of forceps is almost *automatic*. The maneuver has been used for a number of years by the author and some other members of the staff of this clinic with most gratifying results.

The established maneuvers of Scanzoni, Bill, and Kielland, and the key-in-lock rotation for occiput posterior positions have always been felt to have some disadvantages. The most important of these has been the inability to be certain of a perfect cephalic application of the forceps with resultant obvious external damage and bruising of the baby, and less obvious but infinitely more important intracranial injury.

It has been known for a long time that tearing of the tentorium cerebelli is the commonest cause of intracranial hemorrhage in the newborn. Further, it was well demonstrated twenty-five years ago that tearing of the tentorium is accomplished with much less compression pressure applied in an oblique or anteroposterior direction to the cranial vault than in a lateral direction. Thus, any pressure on the fetal cranial vault applied by the obstetrical forceps offers much less chance of tentorial tear if the forceps blades are over the ears in perfect cephalic application. Any method of ensuring such application automatically would appear to offer advantages over other methods.

Most obstetricians, becoming used to one forceps, prefer to use it for the delivery of all vertex presentations. For this reason, as well as for the capacious cephalic curve it possesses, our instrument of choice is the Dewees forceps. Its pelvic curve, properly compensated for during the maneuver, obviates the disadvantages of forceps lacking a true pelvic curve, such as Kielland's instrument.

Method

The usual requirements or conditions before the application of forceps—empty bladder and rectum, fully dilated or dilatable cervix, ruptured membranes, no absolute disproportion, and exact diagnosis of fetal position—must be fulfilled.

^{*}Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynae-cologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario.

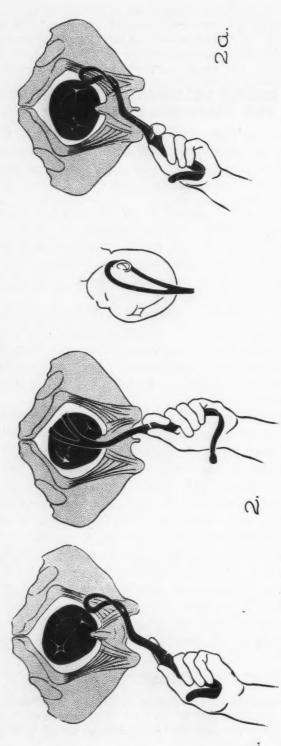


Fig. 1.—The beginning of application of the first blade. Fig. 2.—The first blade catching on the anterior ear. Fig. 2a.—The beginning of application of the first blade for a transverse position.

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The maneuver for rotation of the fetal head is primarily one of a single forceps blade application, applied upside down to the opposite side of the maternal pelvis (i.e., in left occipitoposterior, the right blade to the left side of the pelvis) in such fashion that, on anterior sliding movement, it sweeps over the occiput and catching on the anterior fetal ear rotates it to a position directly behind the symphysis pubis. The movement of this blade into place is, therefore, completely in the direction that rotation of the fetal head is intended, without upward displacement of the head. Secondarily, the other forceps blade is slid into place over the opposite ear by sliding it like a scoop or shovel along the sacral curve. Inasmuch as the first blade is caught on the ear, the second blade is locked to it by depressing the forceps handles and adjusting the second blade to lock with the first. The blades must then each be resting over an ear. By sweeping the handles laterally and anteriorly in a quarter-circle (sometimes with slight pressure in a cephalic direction) the remaining rotation of the fetal head from transverse to occiput anterior position is accomplished easily. Often, then, an adjustment is advisable to flex the fetal head. This is done simply by loosening the forceps lock while fundal pressure is applied, and then tightening it again. The fetus is now ready for extraction from the occiput anterior position. At no time during the maneuver is the fetal head ever pushed up out of the pelvis, the greatest dislodgment being only about 1 cm.

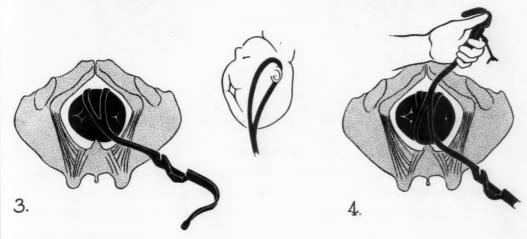


Fig. 3.—Head rotated to transverse position by single blade over ear. Fig. 4.—Application of the second blade.

Fig. 1 shows the beginning of application of the first blade upside down to the opposite side of the maternal pelvis. This blade is partially inserted over the perineum and the handle depressed before full insertion to compensate for its pelvic curve. Its position on complete insertion is just posterior to the occiput.

Fig. 2 shows the position at which the first blade comes to rest when it catches on the anterior ear. Some rotation of the occiput has usually occurred at this time by the anterior sweep of the blade over the occiput. Note the depressed position of the handle.

Fig. 2a shows the beginning of application of the first blade posterior to the occiput in a transverse position.

Fig. 3 shows the position at which the anterior rotation of the occiput by the single blade, caught on the anterior ear, is stopped before application of the second blade. The anterior ear is now directly behind the symphysis with the forceps blade over it between ear and symphysis. Continuing depression of the handle prevents urinary tract or birth canal damage.

Fig. 4 shows the application of the second blade in scoop or shovel fashion along the sacral curve. When fully inserted the handle of this blade must be greatly depressed and adjusted slightly laterally to lock with the first. No adjustment of the first blade should be made.

Figs. 5 and 6 show the continuing and completed rotation of the fetal head to the occiput anterior position with both forceps blades in place and locked. This is accomplished by swinging the handles laterally and anteriorly through a quarter-circle, fitting the pelvic curve of the forceps to the curve of the birth canal.

Hereafter it is well to remember to loosen the forceps lock to allow flexion of the head by fundal pressure before tightening the instrument again for extraction.

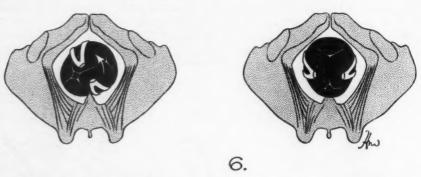


Fig. 5.—Commencement of rotation.

Fig. 6.—Completion of rotation to occiput anterior position.

Advantages

The advantages of this maneuver over others for the rotation of persistent occiput posterior and transverse positions are many:

- 1. A perfect cephalic application of the forceps is almost always automatic.
- 2. External and internal damage to the fetal head is minimized by lateral application of pressure to the cranium and keeping the forceps blades from contact with the face at all times.
- 3. A single application of forceps only is required, minimizing the risk of infection.
- 4. All lateral movements of the forceps are in the direction of intended rotation.
- 5. Slipping of the fetal head back to its original position cannot occur between steps in the procedure.
- 6. Damage to the birth canal is minimized by using a forceps designed to fit it. Damage to the fetus has never been encountered.
- 7. Blood loss is minimized by allowing episiotomy to be delayed until the head is crowning.

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8. The method is extremely simple to use. Our senior house staff prefers it to other methods.

Disadvantages

The disadvantages of the maneuver are very few:

- 1. In the rare case with the fetal head wedged tightly in the pelvis, the head will not rotate easily or satisfactorily.
- 2. In one case where the membranes were ruptured but the amnion was still around the head, rotation did not occur because the anterior blade of the forceps slid over the ear. This, of course, was easily corrected.

Summary

A simple maneuver for the rotation and extraction of persistent occiput posterior and arrested transverse positions has been described. It offers automatic perfect cephalic application of the forceps with resultant avoidance of damage to the fetal head. Results with its use have been most gratifying over a number of years.

Appreciation is expressed to Miss Helen MacArthur for the excellent illustrations.

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HYPOFIBRINOGENEMIA IN PREGNANCY AND THE PUERPERIUM*+

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A CQUIRED hypofibrinogenemia has now emerged from the rarity of isolated case reports as an established concept. The next step is to consider the changes this concept must produce in the management of the syndromes with which it may be associated.

Acquired hypofibrinogenemia has been most constantly found in association with: (1) abruptio placentae; (2) intrauterine death with a macerated fetus; (3) amniotic fluid embolism; (4) delayed postpartum hemorrhage; and (5) severe toxemia of pregnancy.

All these conditions have one significant factor in common. They present the opportunity of the extraction of tissue thromboplastin from amniotic fluid or damaged or necrotizing placental tissue.

Material and Methods

It is the purpose of this paper to present the results of an investigation into the total protein and fibrinogen levels in 45 cases of normal pregnancy, at delivery and on the first, third, and fifth days of the puerperium. An investigation into the fibrinogen levels in 80 cases of abortion, and in each of the first four of the previously mentioned syndromes is also to be reported.

The total protein and fibrinogen levels have been estimated by the micro-Kjeldahl method. The blood has been taken aseptically and all the estimations have been carried out by two experienced technicians.

Results

Total Protein.—The commonly accepted statement with reference to the total protein level¹⁻³ in normal pregnancy is that it decreases gradually as the pregnancy progresses. This decrease is said to amount to 11.5 per cent of the total protein fraction. It is accounted for by a 32 per cent fall in the albumin fraction, offset by a 20 per cent rise in the globulin fraction. These conclusions have been based on single determinations on different women in each trimester of pregnancy. In the present investigation, the total protein levels have been followed in the same patients at first at monthly intervals, and at biweekly intervals in the last trimester.

Most of our determinations gave figures slightly below the normal, until about the thirty-second week, when there was a slight tendency to rise as term approached. All readings were between 5 and 7 Gm. per 100 c.c., the accepted normal being 6 to 8 Gm. per 100 c.c.

^{*}Study supported by a grant from the Department of Obstetrics and Gynaecology, University of Toronto.

[†]Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynaccologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario.

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Fibrinogen Levels in Pregnancy (Fig. 1).—As with the total protein, the levels of fibrinogen have been investigated by determinations made with increasing frequency as term approaches. Estimations have also been made at delivery and on the first, third, and fifth days of the puerperium.

The scattergram shows gradually increasing levels as term approaches, a slight fall at delivery, and then slightly increased levels in the postpartum period. The curve duplicates that obtained by other workers in the field.^{4, 5, 6} The teleological explanation is given that the levels increase in anticipation of trauma and blood loss. The average levels during pregnancy are given in Table I. The average level at delivery is 325 mg. per 100 c.c.

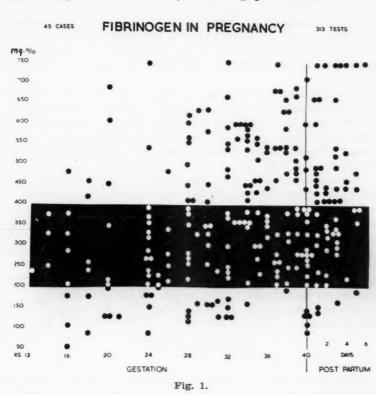


TABLE I. AVERAGE FIBRINGEN LEVELS DURING PREGNANCY

	FIBRINOGEN LEVEL (MG./100 C.C.)	
Week of Pregnancy.—		
18	275	
20	335	
22	_	
24	300	
26	315	
28	360	
30	360	
32	390	
34	455	
36	470	
38	460	
Term	325	
Days Post Partum.—		
1	420	
3	435	
5	440	

Fibrinogen Levels in Abortion.—Eighty cases of abortion at various stages of pregnancy have been investigated. Very little deviation from the normal levels has been found. This confirms statements made by Reid.⁵ The actual average levels are shown in Table II.

TABLE II. FIBRINGEN LEVELS IN ABORTION

GESTATION	NO. OF CASES	AVERAGE FIBRINOGEN LEVEL (MG./100 c.c.)
Up to 12 weeks	59	375
12-20 weeks	21	420

Etiology of Hypofibrinogenemia.—The etiology of the syndrome remains controversial, but is fully covered in the writings of Reid.⁵⁻⁹ The common factor in all these conditions is the ready availability of tissue thromboplastin from damaged decidua or placenta in intimate contact with the open maternal venous sinuses.

Tissue thromboplastin, entering the blood stream, initiates the sensitive blood coagulation mechanism. This causes extensive intravascular clotting with the production of microscopic fibrin emboli and a resultant depletion of blood fibrinogen. These microscopic fibrin emboli end up mainly in the liver and lungs, where they have been found post mortem in cases of eclampsia and abruptio placentae. The sense of eclampsia and abruptio placentae.

Animal experiments using thromboplastin, amniotic fluid, meconium, decidual or placental extracts¹³⁻¹⁹ have all reproduced the syndrome of extensive formation of intravascular microscopic fibrin emboli followed by defibrination of the blood. Page,¹⁸ using radioactive-iodine-tagged thromboplastin, has found that the bulk of the substance ends up in the liver and lungs.

In certain cases, 9, 20 particularly those associated with intrauterine death, a circulating fibrinolysin is reported. It may be postulated that the excessive intravascular fibrin present may stimulate the protective fibrinolysin system excessively in an attempt to keep the circulation free of clots.

Nature of the Coagulation Defect.—From the therapeutic point of view, it is more important to establish the nature of the clotting defect than to determine its etiology. Hypofibrinogenemia seems to be the main factor, but this does not account adequately for all the cases. It may not be the sole defect.

We have observed many cases associated with sudden severe blood loss in which the fibrinogen level is critically low, but in which the blood coagulation proceeds satisfactorily. Jackson and associates²¹ reported a case in which, following an intrauterine death, the fibrinogen level was consistently below the critical value, yet bleeding did not occur at delivery. In their series, they are convinced that unless hypofibrinogenemia is accompanied by serious thrombocytopenia there is no real danger of failure of coagulation.

Seegers²² reported a case of abruptio placentae in which the coagulation defect lay in the Ac-globulin or Factor V. Other authorities^{5, 7, 9, 17} consider that a circulating fibrinolysin is the responsible factor.

In view of these facts, merely replacing the fibrinogen loss may not correct the situation. We must try to replace the entire coagulation scheme in active form.

Principles of Therapy.—When confronted with hypofibrinogenemia we have obtained our best results by rapid administration of freshly taken citrated whole blood. As a precaution, after every 2,000 c.c. of blood we have given 10 c.c. of calcium gluconate intravenously, in order to combat the effect of excess sodium citrate.

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In nearly every case, a large amount of blood has been lost. The danger of overloading with massive rapid replacement is consequently minimal. We have a readily available source of fresh whole blood obtainable from our intern staff. In many series, particularly that of Weber,²³ replacement of fibrinogen in the indicated dose of 4 to 6 Gm. dissolved in dextrose in water has been used exclusively and effectively.

As in most newly described medical syndromes, the more that hypofibrinogenemia is sought after, the more cases are found. Now that fibrinogen is more readily available, there is a temptation to use it when it is not indicated, or perhaps when contraindicated. Bearing in mind the admitted risk of homologous serum jaundice from this preparation, it would be well to caution against its indiscriminate use. We would do better to consider the use of fresh blood as the definitive treatment of hypofibrinogenemia, reserving fibrinogen for emergency use where fresh blood is either unavailable immediately—or ineffective.

Diagnosis.—The diagnosis in these cases is made most practically by use of the clot observation test.

A. Failure of freshly aseptically drawn venous blood to clot when incubated at 37° C. in half an hour, or formation of a normal clot with poor clot retraction and evidence of gross hemolysis in the serum is believed sufficient evidence that the circulating blood fibrinogen is reduced to a critical level. This condition may make effective hemostasis impossible.

B. If the clot when incubated at 37° C. for one hour either disintegrates or dissolves, a low level of fibrinogen also is suggested.

Blood should also be taken for laboratory confirmation of the fibrinogen level, and a platelet count carried out.

Fibrinadex.—The addition of purified human thrombin to the serum of the patient will produce clotting. The rate at which the clot is produced is proportional to the amount of fibrinogen available. More important is the quality of the fibrin clot when compared with that of a control subject. This rapid quantitative test can be carried out by Fibrinadex,* the possibilities of which we are at present investigating. So far, the clinical correlation is reasonably satisfactory, but more work is being done on this problem.

Clinical Discussion

Abruptio Placentae.—Twenty cases of abruptio placentae have been investigated with regard to fibrinogen levels. The normal delivery level was taken as 325 mg. per 100 c.c.

There were 7 cases of mild abruptio placentae, 2 of which were toxemic. The average fibrinogen levels were 460 mg. per 100 c.c. No bleeding tendency was noted in these cases.

There were 13 cases of severe abruptio placentae, 3 of which were toxemic. The average fibrinogen level was 190 mg. per 100 c.c.

Seven patients displayed fibrinogen levels of 150 mg. or below, all of whom gave anxiety by virtue of varying degrees of failure of coagulation.

These figures support Reid's contention that the best classification of abruptio placentae, from the point of view of management, is not on the basis of toxemic or nontoxemic cases, but into those with normally clotting blood, and those in which clotting power is deficient or abnormal. This is illustrated in Table III. It is among the cases with a coagulation defect that the maternal deaths occur. This is either directly from the hemorrhagic tendency, or indirectly from renal or pituitary insufficiency.

^{*}Ortho Pharmaceutical Corporation.

TABLE III, BLOOD REPLACEMENT IN ABRUPTIO PLACENTAE AND FIBRINGEN LEVELS

No. of cases	7	6	7
Fibrinogen levels (mg.)	460	150+	150-
Blood in c.c.	0	1,330	2,500

In the management of the severe cases of abruptio placentae, the following precepts must be stressed:

1. It is generally accepted that once the source of the thromboplastin, i.e., the placenta, is removed, the fibrinogen level will be well on the way to recovery in 2 to 3 hours and completely restored in 12 to 24 hours. Contrariwise, while the patient remains undelivered, she is always in danger from the possibility of incoagulable blood.²⁴ Prolonged delay in delivery is therefore the main danger in these severe cases.²⁵

2. On the other hand, premature operative interference without prior restoration of the clotting mechanism is even more dangerous. The majority of patients can and should be delivered by the vaginal route.

3. Reid⁷ statės that the thromboplastin is squeezed into the maternal circulation by virtue of the fact that the intrauterine pressure, obviously increased in abruptio placentae, is higher than the venous pressure in the uterine sinusoids.

Artificial rupture of the membranes will reduce this intrauterine pressure and prevent further defibrination of the blood. This procedure should be carried out as soon as resuscitation of the patient has been accomplished, without regard for the state of the cervix or the presence or absence of uterine contractions. Cesarean section should be reserved for those cases in which, following this procedure, delivery is unduly delayed.

4. Restoration of the normal state with regard to coagulability of the blood can best be carried out by immediate blood replacement with freshly taken citrated blood. Bank blood is said to be definitely deficient in fibrinogen and therefore fresh blood should be made available in all severe cases. Fibrinogen should always be available and, when used, a dose of 4 to 6 Gm. dissolved in dextrose in water and administered intravenously is indicated. A supply of both should be kept in stock in the obstetrical departments.

5. If the coagulation defect is well controlled, postpartum hemorrhage is rare, and the need for hysterectomy in the treatment of abruptio placentae should not arise. If the defect has not been corrected, hysterectomy is dangerous, merely transferring the source of bleeding from the uterus to the cervical stump, vaginal vault, or abdominal incision.

Intrauterine Death of the Fetus.—

There is general agreement that the main factor in hypofibrinogenemia in association with intrauterine death of the fetus is the absorption of amniotic fluid or degenerating products from the disintegrating fetus which is in contact with the live decidua.^{9, 19, 20} Rh sensitization occurs frequently in these cases, only because this is a common cause of intrauterine death.

Unless determinations of fibrinogen levels are carried out frequently during the time between intrauterine death and delivery, the blood may become silently incoagulable and profuse uncontrollable unexpected hemorrhage may occur at delivery. It may be pointed out of course that the occurrence of defibrination is rare even in the presence of a dead fetus, but this is no reason to relax vigilant observation of fibrinogen levels.

We are reporting 10 cases, 4 intrauterine deaths associated with Rh sensitization, 2 associated with diabetes, 2 with toxemia, and 2 of unknown eti-

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ology. In 2 cases, critical levels were observed about one month before delivery, but recovery of the normal level subsequently occurred. The other 8 cases were associated with normal levels and in these there was minimal bleeding.

Speculation as to why one patient develops the coagulation defect and others do not is interesting. In the majority of cases in which there is no defect, the placenta appears firm and dry, suggesting that the placenta and fetus are retained as an inert mass in the uterus—so dead that nothing can be absorbed from it. More investigation is needed into this aspect of the problem.

In view of the danger of sepsis, there is a natural reluctance to induce labor by rupture of the membranes in cases of intrauterine death. It might be argued, however, that since the development of the hypofibrinogenemia may be proportional to the length of time the dead fetus is retained, the sooner the pregnancy is terminated the better. In 4 of our cases the dead fetus was retained for over thirty days, and in our experience so long as the fibrinogen level is consistently over 150 mg. per cent we can confidently state that no excessive bleeding will occur from this cause.

In view of these factors the better management is based on careful and frequent following of the fibrinogen levels at least twice weekly. So long as the level is maintained, no trouble need be anticipated. If the level falls, the patient should be admitted for daily observation, and adequate quantities of fibrinogen and fresh blood made available for her delivery.

Amniotic Fluid Embolism.—Only one point need be stressed in regard to predisposing factors in these tragic cases. In all, tumultuous contractions, accompanying rapid multiparous labor following rupture of the membranes, have been observed. Careful analysis of individual case reports in the literature^{8, 23, 26, 27} reveals that in almost every case pituitary extract has been exhibited, in the majority of instances in a multiparous labor which was already proceeding reasonably normally. This practice cannot be too strongly condemned.

Delayed or Late Postpartum Hemorrhage.—Delayed postpartum hemorrhage is most often associated with retention of necrotic decidual or placental fragments. The prerequisites are again present for maternal autoextraction. In fact, in our experience and in reports from the literature, coagulation defects have accompanied only this type of postpartum hemorrhage.^{28, 29}

In these cases, bleeding starts typically between the sixth and twelfth postpartum days. An attempt is first made to control it by medical measures, i.e., with Ergotrate and probably without hospitalization. If a coagulation defect is present, this is a dangerous course of action. Not only does it prolong the opportunity for dissemination of thromboplastin, but the production of uterine contractions may definitely hasten the process.

On hospitalization, overanxiety to explore the uterus with a curette, without a preliminary thorough investigation of the hematological status, may greatly increase the bleeding. In the majority of cases, at operation bleeding is found to be coming from a well-contracted uterus, together with oozing from the cervix, vaginal walls, and episiotomy incision. Occasionally, curettage and packing are ineffective, so a hysterectomy is performed, another instance of transfer of the bleeding point.

The logical therapeutic approach to the problem is first to look for a coagulation defect with the recommended tests. If it is present, it must be corrected by rapid transfusion with fresh blood or by the use of fibrinogen. This should be done before the uterus is explored, rather than when we are confronted by the condition as a result of exploration of the uterus. Once

blood clotting is assured, the uterus can be explored safely, and should be explored, in order to remove the necrotic tissue responsible for the situation.

Delayed postpartum hemorrhage is rare, coagulation defect accompanying it is even more rare, so that a high index of suspicion is called for in every case, to be prepared.

Summary

- 1. The total protein and fibrinogen levels have been followed in 45 cases of normal pregnancy, labor, and in the early puerperium. The protein levels show a slightly downward trend with a rise to normal just prior to delivery, the fibringen levels show an upward trend to delivery. The average fibrinogen level at delivery is 325 mg. per 100 c.c.
- 2. Fresh blood is the physiological therapy for coagulation defects during Fresh blood and fibringen should be readily available in obpregnancy. stetrical units.
- 3. The classification of abruptio placentae on the basis of good or poor clotting power of the blood is recommended.
- 4. The necessity for complete restoration of clotting power in these serious cases and the danger of operating before this has been carried out are stressed.
- 5. With a dead fetus, so long as the fibringen level is maintained, interference is unjustifiable.
- 6. The coincidence of the nonindicated usage of pituitary extract and amniotic fluid embolism is pointed out.
- 7. The management of secondary postpartum hemorrhage associated with coagulation defects is discussed.

My thanks are due to Dr. L. T. Armstrong, Chief of the Department of Obstetrics and Gynaecology at the Toronto Western Hospital and to those physicians who allowed me to use their cases. For technical help I am indebted to Mr. R. Boyle, Mr. R. N. Roy, and their technicians, and to Dr. John Gillies.

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THE EFFECTS OF PROLONGED PREGNANCY*

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ESPITE the notorious difficulty of estimating the length of gestation accurately, there are undoubtedly many pregnancies that exceed the usual 280 days. Whether or not such prolongation constitutes postmaturity and, by implication at least, a pathological state is not yet entirely clear. Opinions on postmaturity range all the way from complete denial of its existence to grave concern over what many regard as an established, if poorly understood, clinical diagnosis. Thus Kamperman¹ referred to postmaturity as "a state of mind of the obstetrician," while Holmes2 called it "a figment of the imagination." In a cogent analysis of this problem Wrigley's accepted the diagnosis but emphasized that the duration of the pregnancy past the expected date of confinement is but one of the criteria of postmaturity. Because of this great divergence of opinion and the absence of an acceptable definition of postmaturity, use of the term is avoided in the title. At the Winnipeg General Hospital pregnancies exceeding the estimated date of confinement have never evoked special consideration. The policy has almost invariably been to await the spontaneous onset of labor.

In the past few years many data have been published strongly suggesting that, so far as the fetus at least is concerned, pregnancy going beyond 42 weeks constitutes a complication. Most of these publications originate in the United Kingdom. The present review covers the case records of 1,000 consecutive deliveries on the Public Service of the Winnipeg General Hospital during the years 1952 and 1953. The estimated date of confinement was determined simply by Naegele's rule, though its deficiencies are fully recognized. Twenty-five cases had to be rejected for lack of information. Of the remaining 975 only those of 38 weeks' duration and over were considered, leaving a total of 772 cases. These were divided according to the length of gestation in weeks, all those over 42 weeks comprising a single group.

TABLE I. INFANTS WHO WEIGHED 9 POUNDS OR MORE

		9 POUNDS' WEI	9 POUNDS' WEIGHT OR MORE	
GESTATION IN WEEKS	NO. OF CASES	NO.	%	
40	268	14	5.2	
41	209	24	11.4	
42	132	16	12.1	
43 plus	80 (8.7%)	24	30.0	

Complications of labor do not seem to be increased in spite of the increasing weight of the fetus. In Fig. 1 the average weight is shown to rise from 6 pounds, 11 ounces at the thirty-eighth week to 8 pounds, 5 ounces at the

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^{*}Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynae-cologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario,

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forty-third week and over. The increase in weight from the thirty-ninth to the fortieth week and from the forty-second to the forty-third week and over is significant. More important, perhaps, than the rising average weight, is the increasing number of infants who weighed 9 pounds and over as shown in Table I. Seven of the 80 infants delivered after the forty-second week weighed 10 or more pounds, yet in no instance was this a cause of dystocia.

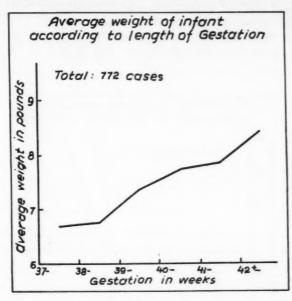


Fig. 1.

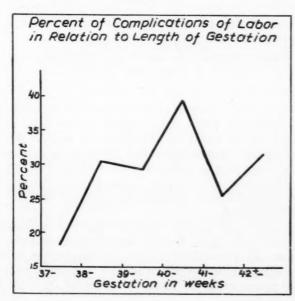


Fig. 2.

In 1952, in an unpublished review⁴ of 898 deliveries on both Public and Private Services at the Winnipeg General Hospital, it was found that the duration of labor was not significantly affected by the length of gestation. In the present series the duration of labor in cases of more than 42 weeks' dura-

tion exceeded 24 hours on 2 occasions. In neither case was this due to the size of the fetus. In Fig. 2 the relationship between the length of gestation and the complications of labor is shown. All forceps deliveries, malpresentations, rotations, prolonged labors, and cases of prolapse of the cord are included in the term "complications." There is no significant difference in the number of complications of labor between the various groups.

The role of the elderly primipara was investigated without establishing any significant relationship with prolonged pregnancy. The ratio of primiparas to multiparas remained approximately 1 to 5 in each group. Among the 80 overdue cases there were 16 primiparas but only 2 of them were over 30 years of age.

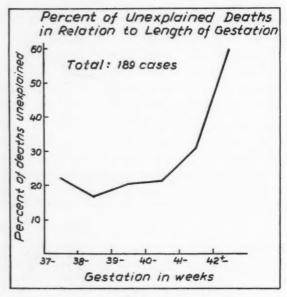


Fig. 3.

It appears, then, that prolonged pregnancy is not a maternal hazard. But is the same conclusion valid with regard to the fetus? In order to investigate this aspect of the problem, all perinatal deaths that occurred from May, 1950, until the year ending December, 1954, were reviewed. These numbered 495 but only those in the thirty-eighth week and over were considered, leaving a total of 189 cases. These were again grouped according to the length of gestation in weeks at the time of delivery. During this same period of time there were 17,052 deliveries.

The fetal mortality rate is generally thought to be somewhat higher in pregnancies that are prolonged beyond the expected date of confinement. This factor was not examined directly but the mortality rate for the 80 deliveries after the forty-second week was 3.75 per cent as compared to the over-all rate of 3.2 per cent in 1952 and 2.8 per cent in 1953 in the Maternity Pavilion.

Fig. 3, however, demonstrates the most startling finding in this analysis, namely, 60 per cent of the deaths that occurred in pregnancies of 42 or more weeks' gestation are unexplained as compared to the average 20 per cent. Unexplained deaths are those in which the pregnancy and delivery as far as

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could be determined were normal and autopsy findings not specific for anything but anoxia. Table II illustrates the distribution of these cases. The percentage of increase in the unexplained deaths after 42 weeks is statistically significant. Six of the 12 unexplained deaths in the 43 week group occurred before the onset of labor; one by 5 days, one by 2 days, and the rest within a matter of hours. Three occurred during labor and 3 infants lived from a few minutes to 8 hours after delivery. In no instance was there a diagnosis of postmaturity made. Unfortunately, there is no record of signs of fetal anoxia, particularly with regard to meconium staining of the liquor amnii.

TABLE II. UNEXPLAINED DEATHS

LENGTH OF GESTATION		UNEXP	LAINED
(WEEKS)	NO. OF CASES	NO.	%
38	18	4	22.22
39	30	5	16.67
40	59	12	20.34
41	33	7	21.21
42	29	9	31.03
43 plus	20	12	60.00

Comment

While prolonged pregnancy does not seem to complicate labor, it is probably inimical to the welfare of the fetus as indicated by the high proportion of unexplained deaths. Walker⁵ has shown what appears to be a definite relationship between the increase in unexplained deaths and the drop in oxygen content of cord blood taken immediately after birth of the infant. The oxygen content decreases slowly at first from about 14 vol. per cent at the thirtieth week to 12 vol. per cent at the thirty-ninth week. Thereafter the fall is very rapid and by the forty-third week the oxygen content of cord blood obtained from the vein is down to about 8 vol. per cent. Postmortem findings in the so-called unexplained deaths are usually those due to anoxia. In all of the 12 unexplained deaths where maceration was not too extensive, anoxia was the common finding at autopsy.

Management

The proper management of pregnancy that has exceeded the expected date of confinement by 1 or 2 weeks seems to be clearly indicated in view of what has just been said. There are, however, other factors no less important than impending fetal anoxia to be considered. In the first place, there is the difficulty of calculating accurately the length of the pregnancy in question. Wrigley³ has advised that each case should be given detailed consideration and be re-examined frequently once postmaturity is suspected. The actual number of weeks past term is not as important as the supposed signs of postmaturity, such as loss of weight, increased muscular rigidity of the fetus, loss of liquor, etc. Most obstetricians, I think, will not find these hints very reliable.

It is for this reason that Racker⁶ suggested that all pregnancies should be terminated no later than the second day after the expected date of confine-

ment. By so doing he reduced the stillbirth rate from 8.72 per cent in pregnancies 14 or more days overdue to 1.47 per cent. In the present investigation, although the number of cases exceeding 42 weeks was small, the total fetal mortality rate was only 3.75 per cent. In none of them was labor induced for postmaturity. Racker stresses that this improvement exceeds any increase in fatalities that might result from prematurity. Walker⁵ gives similar advice and warns in addition of the significance of meconium staining of the liquor. He points out that in pregnancies that are overdue the fetal heart rate is not a reliable indicator of fetal anoxia, and that the appearance of stained liquor is evidence that the fetus has already suffered anoxia. In a primipara over 25, where meconium staining appears and a long labor is anticipated immediate cesarean section should be considered. Clifford's views on the management of overdue pregnancy stress a similarly urgent solution.

Summary

The term postmaturity is used by many to mean at once prolonged gestation and a premature decline in placental function. While placental insufficiency is probably the critical factor in either case, from a practical standpoint it is nevertheless important to state clearly in what sense the term is used.

It is apparent that most of those who have investigated prolonged pregnancy recently see no other course but to induce labor around the forty-second week or even sooner. This policy is probably a good one but only where it is controlled by the very highest standards of obstetrical practice. It is well to recall that it took 17,052 deliveries over a period of four years to collect 12 deaths in infants that might be attributed solely to postmaturity. Further, it seems reasonable to doubt whether Racker's high fetal mortality in pregnancies exceeding 42 weeks is a true reflection of the problem. For this reason alone it seems wise to continue to teach students and our colleagues in general practice that the best management of a case that has passed the forty-second week is to await the spontaneous onset of labor.

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MYOMECTOMY*

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CCORDING to Noble¹ the first deliberate operation for a fibroid tumor was that of Amussat in 1840 and his first paper which was published in 1842 contained the report of two successful cases of vaginal myomectomy. The same author further reports that Washington L. Atlee did the first abdominal myomectomy in 1844, with a successful result. Howard A. Kelly² in his first edition of Operative Gynecology published in 1898 recommended the more liberal use of myomectomy in the treatment of uterine fibroids. He also gave the indications, contraindications, and technique of the operation which was perhaps the first such account to appear in the literature. Up until recent years myomectomy has been a popular operation with relatively few gynecologists. However, such men as Kelly, Noble, Mayo, Bonney, and Rubin have recommended and used extensively this conservative type of surgery in the treatment of the myomatous uterus.

With the ever-increasing problem of infertility, the value of myomectomy is becoming more apparent. For this reason the obstetrician is being confronted by the pregnant patient with a myomectomy scar in the uterus more commonly than ever before. This study was initiated because it was our impression that rupture of such a uterus during pregnancy or delivery is less likely than is generally believed.

This paper is based on a study of 335 cases of myomectomy carried out at The Johns Hopkins Hospital during the years 1930 to 1951. Eighty-eight of these were vaginal while the remaining 247 were abdominal myomectomies. This includes not only cases in which the primary indication for operation was myomas of the uterus, but also those in which the fibroids were coexistent with other pathological lesions.

A follow-up of two years or more was obtained on 234 and of five years or more on 176 of these patients. Of the 335 patients, 172 were white and 163 Negro.

Pregnancy and Myomectomy

Most agree that myomas of the uterus complicate pregnancy in less than 1 per cent of cases and this is borne out by Gainey and Keeler⁶ who report an incidence of 0.5 per cent in 355,550 pregnancies gathered from a review of ten series of cases.

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^{*}Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario.

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Myomas of the uterus predispose to sterility and indeed in this series there were 21 patients whose primary complaint was sterility and whose only abnormality was myomas. The only treatment given these patients was myomectomy with the following results: 11 became pregnant a total of 20 times, with 9 delivering a total of 18 living children.

TABLE I. MYOMECTOMY AND STERILITY

CASES	NO. WHO BECAME PREGNANT	NO. DELIVERED LIVING CHILDREN	TOTAL LIVING CHILDREN
21	11	9	18

Five of these myomectomies were carried out on patients 35 years of age or more and 2 became pregnant.

When all those patients who were unmarried, over the age of 40, or who had sterilizing operations performed were excluded, there were 174 patients who could have become pregnant following the myomectomy. All of these patients were followed two or more years and of these 74, or 42.5 per cent, became pregnant with 64 delivering a total of 111 living children.

TABLE II. PREGNANCIES AFTER MYOMECTOMY

NO. CASES	BECAME	PREGNANT	DELIVERED L	IVE CHILDREN	NO. LIVING
	NO.	%	NO.	%	CHILDREN
174	74	42.5	64	36.8	111

There were 28 cases in which a submucous myoma was removed. In this group only 6 pregnancies occurred following operation and 3 of these ended in abortion.

In the majority of cases fibroids do not interfere with childbirth, and although in early pregnancy they may be found deep in the pelvis, at term they are often high up in the abdomen and entirely free of the true pelvis. For this reason conservative management of myomas during pregnancy is the rule and, even when degeneration occurs, operative interference is avoided if possible. However, occasionally because of torsion, acute degeneration, or infection of myomas during pregnancy, surgical interference is indicated.

fection of myomas during pregnancy, surgical interference is indicated.

There were 16 patients operated on during pregnancy. Eleven of these went to term with the delivery of 10 living children and one stillborn. There were 3 premature deliveries, from which 2 infants survived. Two of the patients of this group aborted following myomectomy. One of these patients who aborted became infected with gas gangrene which resulted in the only death in the series.

All of the myomectomies during pregnancy were carried out abdominally except for one which has already been reported in the literature by Scott and Spence.⁷ In this case a vaginal myomectomy was carried out at twenty weeks of pregnancy. The cervix had been dilated by the submucous myoma and four weeks later the patient had premature rupture of the membranes and delivered a premature infant which did not survive.

We were able to determine the method of delivery in only 12 of the 16 cases. Ten were delivered vaginally and 2 by cesarean section.

TABLE III. MYOMECTOMY DURING PREGNANCY

NO. OF CASES	WENT TO TERM	PREMATURE DELIVERY	ABORTION	NO. LIVING CHILDREN
16	11	3	2	12

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Most agree that the incidence of abortion in patients with myomas of the uterus is increased. There were 8 patients whose primary complaint was habitual abortion and whose only abnormality was myomas of the uterus. The only form of treatment given these patients was myomectomy, and all became pregnant following operation, with a total of 4 term infants who lived, one premature infant who lived, and one stillborn infant, as well as 5 abortions.

TABLE IV. MYOMECTOMY AND HABITUAL ABORTION

NO. OF CASES	BECAME PREGNANT	ABORTIONS	FULL TERM	PREMATURE
8	8	5	4	1

In most cases a history of myomectomy is not an indication for cesarean section because rupture of the uterus through a myomectomy scar is rare. If the wall of the uterus has been definitely weakened by the removal of many myomas or by an infection in the uterine incision, cesarean section is indicated. Thus, unless there has been severe mutilation of the uterus at myomectomy or unless the uterine cavity has been entered and the postoperative course has been febrile, the patient should be allowed to deliver per vaginam. The method of delivery of 120 term infants in this series was vaginal in 96 cases and by cesarean section in 24. None of the uteri ruptured.

Recurrence of Myomas Following Myomectomy

Bonney⁴ reported that in 8 of 210 cases of myomectomy there was a recurrence of the tumors, 6 of these requiring operative treatment. In our study of a group of 58 patients who were followed from two to five years, 11 had a recurrence of the myomas, an incidence of 18.6 per cent. Of these, 6 had hysterectomies because of myomas, an incidence of 10.3 per cent.

There were 176 patients who were followed for five or more years after myomectomy. Fifty-five of these had a recurrence of fibroids, giving an incidence of 31.3 per cent. Twenty-nine of these patients had hysterectomies for myomas, and 8 had hysterectomies for other reasons. In the 234 patients followed for two or more years the incidence of subsequent hysterectomy because of myomas and all other causes was 18.4 per cent. Sixty-six of the 234, or 28.2 per cent, had a recurrence and 35, or 14.9 per cent, had a subsequent hysterectomy for recurrence of myomas.

TABLE V. RECURRENCE AND HYSTERECTOMY FOLLOWING MYOMECTOMY

	RECURRENCE		HYSTER	RECTOMY
	NO.	%	NO.	%
58 patients followed 2 to 5 years	11	18.6	6	10.3
76 patients followed 5 or more years	55	31.3	29	16.5
234 patients followed 2 or more years	66	28.2	35	14.9

Contrary to general opinion the incidence of recurrence of myomas following myomectomy was no greater in the Negro patients than in the white.

Table VI. Recurrence and Hysterectomy According to Race (Patients Followed 2 to 5 Years)

		RECURRENCE	E OF MYOMAS	HYSTER	RECTOMY
	NO.	NO.	1 %	NO.	%
White	30	6	20	3	10
Negro	29	5	17.2	3	10.3

TABLE VII. RECURRENCE AND HYSTERECTOMY ACCORDING TO RACE (PATIENTS FOLLOWED 5 OR MORE YEARS)

		RECURRENCE	OF MYOMAS	HYSTER	RECTOMY
	NO.	NO.	%	NO.	%
White	90	28	31.1	15	16.6
Negro	86	27	31.4	14	16.3

Bonney believed that seedling myomas did not appear after the age of 30, and that if a myoma appeared after this age it was probably simply further growth of a seedling that had been present prior to age 30.

Our study does not entirely support this view. The incidence of recurrence in patients operated on over the age of 35 was less (23.3 per cent), however, than when the patient was operated on under 35 years of age (31.3 per cent). The subsequent hysterectomy rate was also reduced in the group who had a myomectomy over the age of 35.

TABLE VIII. RECURRENCE AND HYSTERECTOMY ACCORDING TO AGE

	RECURRENCE OF MYOMAS		HYSTERECTOMY	
	NO.	1 %	NO.	1 %
144 patients under age 35	45	31.3	24	16.7
90 patients 35 or over	21	23.3	11	12.2

The average time between myomectomy and hysterectomy for myomas was 6.9 years.

Complications

In this series of 335 myomectomies, there was one death, giving a mortality rate of 0.3 per cent. As has been previously mentioned, this was the result of gas gangrene infection in a case of abortion which followed myomectomy during pregnancy. A second patient died undergoing anesthesia for hysterectomy for myomas, eight years following myomectomy. One patient had intestinal obstruction ten months after myomectomy. This was corrected by operation and the patient had an uneventful recovery. Two patients developed carcinoma of the cervix following myomectomy, one two years after the operation, and another fourteen years. Both of these patients are still alive. One patient developed carcinoma of the corpus nine years following myomectomy. This patient was given preoperative irradiation plus hysterectomy and is alive at the present time. Only one myoma which was removed showed sarcomatous change, an incidence of about 0.3 per cent. This myoma was submucous in location, and was removed per vaginam. The patient was given irradiation; she died five months later, however.

Even though a patient does not become pregnant and a second operation becomes necessary it does not always mean that myomectomy was a failure, or that a hysterectomy should have been done. Several patients, 2 of whom were physicians, indicated that although pregnancy did not follow myomectomy they still were very satisfied that conservative surgery had been given a trial. They felt there was an important psychological effect produced by the knowledge that pregnancy was still possible. Although patients often fully realized that conception was remote, the small ray of hope which was made possible through the preservation of the uterus helped to maintain a sense of well-being in their psyche.

Summary

There is an increasing demand for conservative therapy in the treatment of myomas of the uterus and rightly so. The main reason for abdominal myomectomy instead of hysterectomy for myomas is to preserve the childbearing function. Thus it is obvious that abdominal myomectomy should be carried out only on patients under 40 and very rarely on patients over 35 years of age. The success of the operation is borne out in this series by the fact that of 174 patients 36.8 per cent became pregnant and delivered living children.

There are few contraindications to abdominal myomectomy prior to the age of 40. In the case of pelvic cancer, however, or great numbers or great size of myomas, or advanced pelvic inflammatory disease, some other form of therapy is more acceptable. Some gynecologists have reported removing great numbers of myomas, at a single operation, perhaps the greatest being Bonney's report of 125, but such enthusiasm is not shared by us. From this study and from reports of others we conclude that there is only slight danger of rupture of the uterus through a myomectomy scar. It seems that unless the uterus has been severely mutilated or there was evidence that the uterine incision was infected, the patient should be delivered per vaginam. Myomectomy during pregnancy should be avoided if possible; however, this will have to be undertaken occasionally. Our report and that of others8 indicate that abortion may occur, but usually the pregnancy continues to term.

From this study it appears that the removal of a submucous myoma is rather infrequently followed by a successful pregnancy.

The recurrence rate of fibroids after myomectomy is somewhat higher than most have believed. There was a recurrence rate of 28.2 per cent in the group followed two or more years, and in the same group subsequent hysterectomy was necessitated by recurrence in 14.9 per cent. From this it is obvious that before undertaking a myomectomy one should be prepared and also prepare the patient for the possible necessity of further surgery.

Race seemed to have little bearing on the recurrence of myomas after myomectomy; age, however, did appear to have some influence.

Myomectomy, both vaginal and abdominal, occupies a very important position in the treatment of myomas of the uterus in the patient under 40 years of age. The results are good and, contrary to the opinion of a previous era, the mortality rate is no greater for this operation than for hysterectomy.

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TECHNICAL DIFFICULTIES OF RADICAL HYSTERECTOMY AND PELVIC LYMPHADENECTOMY*

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URING recent years there has been a revival of interest in the surgical treatment of carcinoma of the uterine cervix. For the last thirty years reliance has been placed to such an extent upon radiotherapy in the treatment of this disease that the surgical approach has fallen into relative obscurity. It was thought therefore that some interest might be engendered if the technical difficulties encountered during operation were presented. This dissertation does not deal in any way with selection of treatment, either radiological or operative.

In the early part of this series of fifty-two cases, patients were chosen carefully for their asthenic build; later, as experience was gained, it was found that even grossly overweight patients could be operated upon with safety, as well as those with either diabetes or arteriosclerotic hypertension, although the latter type of case frequently is subject to sudden falls in blood pressure during operation.

The Operative Team.—There has been a considerable amount written concerning the hospital criteria necessary for the performance of this operation and certainly a high basic standard is necessary, of both operating room, recovery room, and ward personnel. The staff of the usual university hospital can be developed in a surprisingly short time, however, to the point where these operations may be performed routinely. From our experience, it seems desirable that two main conditions be established. First, a permanent operating team should be developed, and, second, the team should spend a considerable amount of time performing dissections of the region on fresh cadavers. This was our policy throughout and many difficulties in technique were surmounted directly by lessons learned from dissection of cadavers, which was found to be invaluable. Thus, all members of the team become equally acquainted with the operative detail as well as the possible hazards.

Preoperative Studies.—A complete clinical and laboratory investigation is obviously a necessary prerequisite of all elective surgery. Antibiotic and chemotherapy to sterilize the bowel are necessary. Cystoscopy should be included in the investigation of the renal tract and ideally should be performed by the gynecologist who is to operate. Intestinal decompression commenced twenty-four hours prior to the surgical intervention prevents intrusion of small intestine into the field at operation.

The Incision.—Two methods of incision of the anterior abdominal wall are available, the transverse muscle-cutting approach or a modified longitudinal midline incision in which both rectus muscles are hemisected. While the transverse incision gave the best exposure of the pelvis, this advantage was nullified by too

^{*}Presented at the Eleventh Annual Meeting of the Society of Obstetricians and Gynae-cologists of Canada, June 17, 18, and 19, 1955, Huntsville, Ontario. **Assistant Professor of Obstetrics and Gynaecology, University of Ottawa.

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frequent superficial wound breakdown in the postoperative period, particularly in obese individuals. This approach was discarded, therefore, in favor of the modified longitudinal incision.

Injury to Pelvic Organs .-

Veins: The common external or internal iliac veins are subject to injury as the lymphoid and fibroadipose tissue surrounding them is dissected free. Small tears of any of the vessels may frequently be closed by lateral ligation. In our series this accident occurred not uncommonly and almost all vessels in the pelvis have been ligated on occasion. Little permanent damage appears to result.

During dissection of the deeper parts of the lateral pelvic wall the thin-walled tributaries of the internal iliac vein are encountered and troublesome hemorrhage results if these vessels are entered. Slow, painstaking dissection is necessary whereby each vessel is sought for and ligated individually before it is sectioned. Although this portion of the operation is tedious and time consuming it is better to proceed thus than to damage one of these vessels and spend considerably more time searching for a venous bleeding point in an ever-present pool of blood. Hemorrhage from these vessels can be severe and difficult to control accurately.

Arteries: Dissection of tissue from around the common and external iliac arteries should be carried out most carefully since at all cost damage to these vessels must be avoided. Constant fear of such an eventuality prompted our team to become proficient at arterial anastomosis and autogenous venous graft replacement from the saphenous vein, by practice on the fresh cadaver. Should these vessels be cut or torn re-establishment of continuity must be accomplished. It is unreasonable and possibly unpardonable to ligate these vessels since gangrene of the limb involved will occur in over 60 per cent of such cases.

The anterior branches of the internal iliac artery are sectioned deliberately by some surgeons, while others prefer to ligate only the uterine branches. Both techniques were employed by our team. Better exposure of the deeper parts of the pelvis results if all the terminal branches of this vessel are excised. No permanent damage appears to result.

The obturator artery may be sectioned purposely or accidently during dissection of the obturator fossa. This need not cause concern provided that the distal fragment of the vessel does not retract deeply into the obturator canal. This occurred in one of our cases and a very considerable amount of time was lost before the hemorrhage was arrested.

Nerves: The obturator nerve is the one most likely to be injured. It lies embedded in the lymphatic and fibroareolar tissue of the obturator fossa and occasionally may be difficult to differentiate from its accompanying artery. Identity of the nerve may be confirmed by compressing it lightly with dissecting forceps when the adductor muscle group that it supplies will contract and cause the leg involved to flex sharply. Section of the nerve occurred several times in our series with no subsequent impairment of locomotion.

The urinary bladder: This organ may be injured when its posterior wall is separated from the anterior cervical wall early in the operation. Should tearing of the vesical wall occur it may mean that unsuspected carcinomatous infiltration of the bladder musculature is present.

It was found that one of the most difficult parts of the operation was the dissection and cleansing of the lateral and posterolateral vesical walls, since it is difficult frequently to define where retroperitoneal fibroadipose tissue terminates and where bladder musculature commences. On several occasions the bladder was opened accidently, due to an overdiligent attempt to remove

the attached fibroadipose tissue. At one stage consideration was even given to performance of routine suprapubic cystostomy so that direct vision might aid lateral vesical wall dissection. However, investigation on the cadaver, so often resorted to in an attempt to solve our operative problems, did not demonstrate that advantage would be gained by this maneuver and the idea was therefore rejected.

Closure of the vesical wall after injury was performed according to standard procedure and was followed by intravesical injection of methylene blue solution, in order that the integrity of the vesical suture line might be tested and any unsuspected fistulas or weak areas demonstrated. This procedure was found to be most useful. In the series two vesicovaginal fistulas occurred; one healed spontaneously, the other was repaired. It is thought that both vesical defects were caused by perforation at operation, which was unnoticed, rather than by sloughing of the wall during the postoperative period. Both occurred before intravesical methylene blue was used as a medium for testing vesical integrity and both occurred in the immediate postoperative period.

The ureters: Preoperative excretory urograms and cystoscopy are not only necessary to demonstrate vesical and ureterorenal pathology but also to note the presence of multiple ureters. The latter are commonly found and cause no inconvenience provided their presence has been established previously.

At operation catheterization of the ureters has been condemned by some authors. Owing to this attitude it was not done in our earliest cases. Soon the use of ureteral catheters was introduced and, proving to be of inestimable value, became standard procedure. The catheters stiffen and splint the ureters and facilitate particularly the definition of the triangular flared-out ureterovesical junction. This area we found difficult to identify and were often in fear of cutting the ureter at this point until ureteral catheterization was adopted, after which this part of the operation became much easier. Occasionally the ureter may be difficult to differentiate from an artery. Stimulation of the ureter results in typical vermiform peristalsis.

Postoperative ureteral fistulas have been reported by Meigs¹ and others. This was not our experience; only one such fistula occurred in our series and it is believed that this low figure is due to the fact that an indwelling urethral catheter was left postoperatively in the bladder for seventeen days as a routine. This was commenced very early in the series to prevent development of an atonic bladder and to discourage the formation of vesical fistulas. It is submitted that, accidently, this contributed to the low fistula rate in the fifty-two cases operated upon. It was policy also, however, never to disturb the fibrous sheath surrounding and clinging to the ureter, within which runs its immediate blood supply. Since this sheath is almost never involved by carcinoma even in the most advanced cases,² there appears to be no compulsion to remove it.

Meigs states that in fifty cases operated upon since 1952 only one ureteral fistula occurred and in this case there were complicating factors. He attributes the lessening of the fistula rate as being due to long-term bladder drainage when no overdistention of this organ occurs and thus mechanically the ureter is undisturbed in its newly formed tissue bed and rapidly gains additional blood supply which is sufficient to prevent any necrosis of its wall. Our observations seem to be in agreement.

The rectum: The rectum may be injured when the pouch of Douglas is opened initially or a longitudinal strip of the anterolateral wall may be included in the clamp crushing the uterosacral ligaments and thus excised with them. This occurred once; however, the defect was closed in layers and a large-caliber rectal tube was inserted from below up past the suture line,

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to ensure regional decompression. It is frequently difficult to differentiate the uterosacral ligaments from lateral rectal wall, but dissection of cadavers demonstrated that if the finger is glided firmly down the lateral rectal wall the uterosacral ligament may be separated completely from its fine attachments to bowel and thus may be isolated and excised close to the sacrum without the use of clamps, which may endanger the integrity of the rectum.

Operative and Postoperative Shock.—During the earlier period of development of our team, shock was a complicating factor in many cases. As experience was gained, alarming falls in blood pressure became correspondingly less common.

Scrupulous avoidance of hemorrhage, the avoidance of traction of pelvic viscera, and the gentle manipulation of abdominal retractors contributed. Sharp dissection was favored whenever possible since both shock and transfusion requirements were definitely less than in those cases where the tissues were exposed predominantly to blunt dissection.

Blood pressure and pulse rate recordings at ten-minute intervals permit the circulating blood volume to be kept at an approximate physiological normal by prophylactic rather than curative transfusion.

The anesthetist was regarded as the most important member of our team and his accurate control of both anesthesia and blood volume requirements was responsible for the fact that less shock occurred in our later cases.

Ten minutes prior to impending amputation of the uterus and associated tissue from the lower part of the vagina, the anesthetist should be consulted, since rapid prophylactic transfusion of whole blood will minimize shock caused by unavoidable traction on the pelvic viscera.

Postoperative shock may occur as pure shock from anesthesia or from intra-abdominal retroperitoneal hemorrhage. The differentiation of pure shock as opposed to shock from hidden hemorrhage is not easy in the immediate postoperative period, and this problem caused some concern. If two Penrose drains are led from the raw retroperitoneal pelvic area through the vagina to the exterior, however, any reactionary hemorrhage will immediately become visible at the vulva, especially if intra-abdominal tension is raised by manual pressure on the lower part of the anterior abdominal wall.

Summary

The various difficulties that may present themselves during the radical operation for cancer of the cervix have been discussed and an attempt has been made to describe their circumvention. No death occurred in this series of fifty-two cases.

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Original Communications

IMPORTANCE OF NUTRITION IN THE IRRADIATION TREATMENT OF CERVICAL CARCINOMA

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WE HAVE been impressed with the average physician's indifference to the nutritional state of the patient with cervical cancer who is treated with irradiation. Malnutrition and anemia appeared to be a reason why some patients were unable to tolerate adequate treatment. These impressions were confirmed in part by a previous analysis.³

References concerning the relation of the patient's nutritional state to irradiation treatment were requested of the American Cancer Society and librarians of the American College of Surgeons, the University of Tennessee, and the Knoxville Academy of Medicine. These sources were unable, however, to supply us with such studies. For this reason, a clinical study was undertaken to ascertain the relationship between the patient's nutritional state and the toleration of irradiation treatment for cervical carcinoma. Particular attention was given to anemia, gastrointestinal disturbances, and vitality. It is recognized that the résumé is incomplete because many natural variables influence the outcome. Statistically, this report is considered acceptable only as a case study. Nevertheless the results support certain conclusions generally applicable to the kind of patient described.

Subjects

One hundred ninety-three patients with cervical carcinoma constitute the material studied. They fall into three groups according to availability of a balanced diet, blood transfusions, and hospitalization. Women in each series were treated consecutively within the period March 1, 1949, to Sept. 1, 1953 (Table I).

TABLE I. PATIENTS DIVIDED ACCORDING TO AVAILABILITY OF BALANCED DIET, BLOOD TRANSFUSIONS, AND HOSPITALIZATION

GROUP	NO. PATIENTS	BALANCED	BLOOD TRANSFUSIONS	HOSPITALIZATIONS
A	142	No provision	As emergency	Only for radium ap
В	29	Special instruction	Hemoglobin maintained	Only for modium or
C	22	Provided	f near normal	Entire treatment

Group A women were indigents treated largely as outpatients through limited welfare funds. Group B were private patients treated largely as outpatients. Group C were semi-indigent and treated as private patients under an insurance plan.

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The average age of women in each group was near 50 years with a range of 25 to 73. Most were native of either the eastern section of the State of Tennessee, the southeastern part of Kentucky, or the southwestern region of Virginia. Nearly all were married and parous. Those with a hemoglobin below 70 per cent, totally or nearly edentulous, more than 10 per cent under their usual weight, and with or without other evidence of malnutrition were regarded as being in poor condition. Those with a hemoglobin of 70 per cent or above, nonedentulous, and less than 10 per cent under their usual weight or overweight, or those with none of these findings were classified as in fair to good condition. Those with incomplete data were unclassified. Further breakdown of the nutritional state was impractical (Fig. 1).

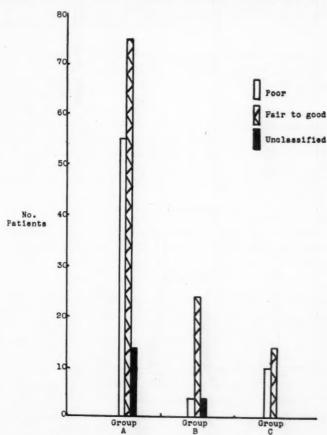


Fig. 1.—Physical condition of patients at beginning of treatment.

The body weights of the patients are given in Fig. 2. The relation and range of the patients' ages to body weight were approximately the same in each group.

Treatment

Each woman had a urinalysis, serologic tests, cervical biopsy, blood count, and most of them had a roentgenogram of the chest. Intravenous pyelograms

were obtained for those with suspected urologic complication or those to be subjected to pelvic dissection.

Irradiation.—The average woman usually received 2,100 r measured in air through each of four pelvic ports, 15 by 15 cm. Two were anterior and two posterior. Patients who were large in girth generally received additional irradiation to each lateral aspect of the pelvis. A few women were given x-ray transvaginally where application of radium was impractical. The usual dose of intracavitary radium varied from 5,500 to 6,500 mg. hr. The milligram hours were usually reduced to roentgens in order to estimate proper distribution for cancerocidal purposes. X-ray and radium applications were contiguous and were usually concluded within an interval of four to six weeks.

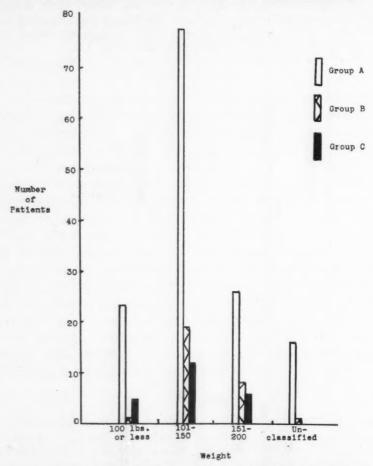


Fig. 2.—Body weights in pounds at beginning of treatment.

Surgery.—Six women in Group B and 9 in Group C were subjected to radical pelvic dissection five to six weeks post irradiation.

Transfusions.—Group A women received blood transfusions during treatment in case of severe hemorrhage or if the hemoglobin was below 60 per cent. Blood for these patients was unavailable, otherwise. Patients in Groups B and C received blood as necessary to maintain the hemoglobin at 80 per cent or above during treatment. Nearly one in 4 of Group A, a third of Group B, and nearly all of Group C women were given a total of 500 to 3,000 c.c. of blood each, exclusive of transfusions for surgery.

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Diet.—Group A patients usually subsisted on a diet either low in protein, iron, calorie, and fat content, or high in carbohydrates and low in protein as calculated from recorded dietary histories for a part of the group. Information for some others was procured either through visits to the patient's home by a public health nurse or direct questioning of the patient by a physician (Table II).

TABLE II. CONTENT OF DIETS OFFERED

DIETARY DATA	GROUP A	GROUP B	GROUP C
Calories	1,600-1,800	2,500-3,000	3,000
Protein (grams)	50-60	100	100
Carbohydrates (grams)	200	300	320
Fat (grams)	76	145	145
Iron supplement	Seldom	Daily	Daily
Vitamins A, D, C, and B supplement	Seldom	Daily	Daily
Method of measurement	Dietary* histories analyzed	Estimation and avoirdupois	Avoirdupois

*Leichseuring, J. M., and Wilson, E. D.8

Dietary instruction was seldom available for women in Group A. In the other hand women in Groups B and C were instructed both by a dietitian and the attending physician to take a high calorie, high protein, balanced diet supplemented with iron during and after treatment. Also, a relative of each patient was taught the importance of the patient's food intake and was enlisted to help preserve the patient's morale. Group C patients were usually given five feedings a day while hospitalized. If they are poorly 5 to 10 units of insulin was given before meals three times a day to stimulate the appetite. The debilitated women received amino acids and vitamins and blood to correct anemia until there was improvement in the appetite.

Pathology

One hundred and ninety-one women had epidermoid carcinoma and 2 others an adenocarcinoma of the cervix. The clinical grade of the tumor is shown in Fig. 3.

Results

Gastrointestinal Disturbances.—Varying degrees of proctosigmoiditis occurred temporarily in all patients who weighed less than 150 pounds and most of those who weighed more than 150 near the end or shortly after treatment was completed. Those who weighed 100 pounds or less suffered most. The leptosomatic were affected more often than the pkynic women.

At this reporting, factitial reactions in the bowel were limited almost entirely to Group A women. They occurred seldom in the well fed, well nourished. In contrast, they were rather frequent among the ill nourished, ill fed. We believe that nutrition is an important all-inclusive causative factor but, so far, we have been unable to prove it. Technical problems associated with the application of the radiation makes this evaluation difficult and controversial.

Women who ate regularly, had no anemia, and had a good intake of food usually remained better nourished, and had less nausea, anorexia, and debilitation than did those who ate irregularly, were anemic, and had a low intake of food. Recuperation was ordinarily accomplished more quickly by the well-fed, wiry woman than by the thin, ill-nourished or obese, poorly fed woman.

Comment: Most patients, at first, refused to eat all of the food set before them. Within a few days, with much urging, however, most of them ate nearly

all their food. The use of bitters, small amounts of insulin before meals, and desirable, easily assimilated food given in frequent small feedings were the most helpful in improving the appetite of the average patient. Intensive administration of blood and amino acids (100 Gm. or more a day) parenterally was required, in addition, for the severely anemic and malnourished woman before there was improvement in the appetite. Patients with a long-continued bodily weakness due to malnutrition not uncommonly appeared to have a poorly functioning gastrointestinal tract unrelated to irradiation treatment. Their appetites commonly remained poor even after anemia was corrected by blood transfusion or forced feedings were given. Wiley and Sugarbaker¹⁴ have made similar observations.

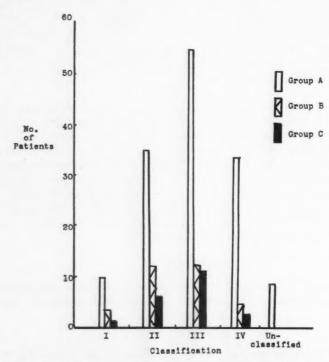


Fig. 3.—Clinical grading of the tumor by the Schmitz classification.

Vitality.—Treatment was protracted or uncomplicated (Table III) for one of every 13 women in Group A, one of Group B, and none of the Group C women because of lack of vitality. It is significant that none of the Group C patients failed in this respect, even though nearly half of them were initially as severely ill and malnourished as the worst of those in series A. In a number of instances supportive treatment and care in the hospital appeared to make the difference between the patient's being able to complete treatment and not being able to

TABLE III. VITALITY AND PROTRACTED OR INCOMPLETE TREATMENT

GROUP	TREATMENT PROTRACTED OR INCOMPLETE	TREATMENT COMPLETED SATISFACTORILY
A	11	131
В	1	28
C	0	22
Total	12	181

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Group A women lost weight more frequently during treatment (sometimes as much as 30 per cent of their original weight) than did Groups B and C patients. Irradiation was apparently a causative factor in precipitating early death from ulcerative intestinal lesions in 3 patients. These lesions were neither obstructive nor neoplastic. In two other Group A women the nutritional state deteriorated to such an extent that intensive dietary measures were required for several weeks to rehabilitate them. There were no such deaths or deteriorations in Groups B and C.

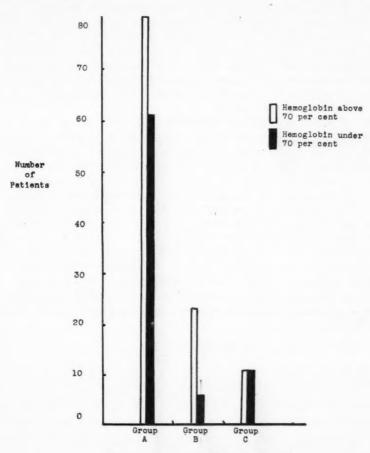


Fig. 4.—Anemia at first examination.

The elderly women tolerated treatment nearly as well as the young women provided they were rendered free from decrements and insufficiencies.

Comment: Frequently the treatment of cancerous women is focused on the extent of the disease and not the state of the patient.^{2, 10-13} Those with growing malignancies usually utilize more nitrogen, phosphorus, and potatssium than other kinds of patients. Transfer of nitrogen from the host to the tumor occurs to attempt to meet the needs of both even though the diet is inadequate.⁴ Derangement of protein metabolism impairs healing of wounds, increases susceptibility to infectious complications, and promotes functional disturbances in the liver and intestinal tract.⁵ Two to three times the amount of protein required daily for a normal person is recommended for the cancerous patient. This in-

take spares protein in the body tissues. In the presence of anemia the replacement of hemoglobin appears to have first call, blood plasma next, and then cellular tissues.^{4, 13}

Anemia.—Two of every 5 Group A, one of 5 Group B, and one of every 2 Group C women had a hemoglobin below 70 per cent at the first examination (Fig. 4). The most severe anemias were seen in Groups A and C with the hemoglobin below 30 per cent in some instances. Women in good physical condition and receiving an adequate diet usually maintained a normal hemoglobin without benefit of transfusion. If the intake of food was poor, patients with a normal hemoglobin at the onset of treatment often proved to be anemic at the end of therapy. Still others anemic and treated with supportive measures at the onset usually needed to have repeated blood transfusions even though special attention was given to dietary measures. Those whose blood picture was maintained near normal usually recuperated more favorably after irradiation as opposed to the anemic women given inadequate supportive treatment. The latter commonly required six months or more while the former generally required only a few weeks to recuperate.

Comment: Fowler and Barer⁶ observed that the average blood donor required 50 days and 25 per cent nine weeks to correct a 2 to 3 Gm. deficit of hemoglobin after giving 550 c.c. of blood at a single donation. "It is understood that normal erythropoiesis requires a number of essential nutritional elements as well as a bone marrow with adequate capacity. It is not well understood that normally the concentration of red blood cells in the circulation is limited by the concentration of hemoglobin in the peripheral blood and not by lack of various endocrines or nutrients."^{1,4} Decreased production of red blood cells in patients with cancer is largely due to bleeding which results in external loss of the iron-containing fraction of the red cell. Sometimes specific nutritional therapy is ineffective in combating anemia in the presence of cancer but without external loss of blood. Then "toxic" inhibition of erythropoiesis must be considered. For this reason it is occasionally a practical necessity to give blood transfusions to those patients who are anemic and in whom substitution therapy is ineffective.

Comment

This study is not large enough to justify any conclusion one way or another as to the effect of nutrition on the curability rate of patients with cervical cancer. We agree with McKelvey.⁹ A massive analysis, probably over a long period of time, would be required to prove that certain dietary measures were important from the standpoint of curability for patients with pelvic cancer undergoing irradiation therapy.

There are certain advantages to inpatient care over outpatient care for the entire treatment. Side reactions to therapy are better controlled. The intake of food is governed more easily. Treatment is uncompleted or protracted less frequently. On the other hand, however, at this reporting hospitalization for the entire treatment of all cancer patients is economically impractical in our community. The cost for the ambulatory inpatient is approximately three times that for ambulatory outpatients.

It is not the purpose of this discussion to give the relative food values in terms of energy and tissue building. Instead, it is the desire to emphasize that the undernourished woman with cervical cancer allowed to remain ill nourished becomes weakened and nonresistant to her disease and is more likely to acquire

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certain complications during irradiation treatment than is the treated wellnourished woman with cervical cancer. Apparently a well-nourished patient or an ill-nourished woman given intensive supportive treatment is less likely to acquire these disorders. An increase in the intake of food probably stimulates cancerous growth little, if any. Nourishment should consist of good, plain, easily assimilated food with a high protein content supplied in ample amounts and attractively prepared to bring alimentary comfort. "That means good appetite, regular bowel movements, stabilized weight and the restoration that comes with sleep and exhilaration that follows excessive useful work." This is such a large order that often most of us have a desire to disregard it. The quality and quantity of the diet should be constantly supervised by the attending physician in conjunction with a dietitian because preferences for various foods, habits of people, and foods produced by different soils are decidedly not standard.

Conclusions

Patients hospitalized for their entire treatment, given a balanced diet high in protein, iron, and calorie content, and transfused liberally with blood to correct anemia tolerated irradiation treatment better than did those not hospitalized or those given inadequate supportive therapy. This was true irrespective of the clinical stage of the tumor.

Those poorly nourished who weighed 100 pounds or less suffered more often and more severely from proctosigmoiditis, anorexia, and loss of weight than did those who weighed more than 100 pounds.

The undernourished woman treated with irradiation and without supportive measures suffered loss of vitality, and acquired anemia more often than did the well-nourished or the ill-nourished patient who received supportive measures. Poor vitality was one of the reasons treatment was sometimes protracted and presumably it predisposed to an occasional early death in the patient given irradiation.

The elderly woman tolerated treatment nearly as well as the young patient provided decrements and insufficiencies were corrected.

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VAGINAL METASTASES FOLLOWING TREATMENT OF ENDOMETRIAL CARCINOMA

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THERE are few reports in the literature dealing with the occurrence of metastatic lesions in the vagina stemming from endometrial carcinoma. These studies have been concerned with such features of metastases as exact location in the vagina, the histological nature of the primary neoplasm, the route of metastasis, therapy, and results of treatment for these secondary lesions.

In preparing this report, we were primarily interested in the incidence of vaginal recurrence following the various methods of treatment of endometrial carcinoma. Only patients who received therapy at the University of Michigan were considered. Only those treated during the period from January, 1930, through December, 1949, were included. This allowed five years or more for follow-up on all patients, a necessity in determining recurrences following treatment for any carcinoma.

Material

Incidence.—A total of 278 patients with untreated endometrial carcinoma were admitted during the previously mentioned twenty-year period. Vaginal metastases or recurrences were encountered in 15 patients, or 5.4 per cent of the total. Of these 15 patients, 7 had vaginal lesions at the time of original admittance to the hospital while 8 developed recurrences after treatment of the primary endometrial carcinoma. This total incidence of 5.4 per cent is less than the 17.7 per cent incidence reported by Way⁵ or the 12.1 per cent in Meigs' series.

All of the carcinomas in our series were of the glandular type. In many cases, no reference to the degree of dedifferentiation of the neoplasm was noted by the pathologist. In others, the terms "poorly differentiated" and "well differentiated" were used. Occasionally Broder's grading was applied. In general, Broder's Grades I and II implied a well-differentiated carcinoma, while Grades III and IV were poorly differentiated.

Histology.—The carcinomas exhibiting metaplasia to the squamous type are of some interest because of Way's contention that these neoplasms are more likely to give rise to vaginal metastases than the pure adenocarcinomas. The degree of squamous metaplasia in a given neoplasm is difficult to evaluate, for small areas of such metaplasia in endometrial carcinoma are not uncommon. In this report, only those carcinomas with marked squamous metaplasia, the acanthoadenocarcinomas, were included in this category. A summary of the histological features of the primary neoplasms and the incidence of vaginal metastases or recurrences in each group are shown in Table I. The data suggest that there is a higher incidence of metastases in the less well differenti-

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ated carcinomas. More striking is the relatively high incidence of vaginal lesions in patients in whom the primary carcinoma exhibited a marked degree of squamous metaplasia.

Table I. Relationship of Differentiation of Endometrial Adenocarcinoma to the Incidence of Vaginal Metastases

TYPE	NUMBER	PER CENT	VAGINAL METASTASES	PER CENT
. Unclassified	52	18.7	0	0
. Well differentiated	151	54.3	3	2.0
3. Poorly differentiated	50	18.0	5	10.0
Marked squamous metaplasia	25	9.0	7	28.0

Location of Metastasis.—The location of the vaginal lesion was of interest. Authors who have previously reported on this subject have differed in their experiences with respect to the exact location of the metastatic lesions. Rickford found 9 cases of vaginal involvement in his series, 7 of which occurred in the vault of the vagina. In Meigs' study, most vaginal lesions were found on the anterior wall halfway between the external urinary meatus and the anterior fornix. The report of Way agrees with that of Meigs but is even more striking in that 13 of 14 vaginal metastases from endometrial carcinoma occurred beneath the urethra within 1 cm. of the introitus. Our series also demonstrates a predilection for the anterior vaginal wall as well as the lower third of the vagina (Table II).

TABLE II. SITE OF VAGINAL LESIONS

Upper third	4			Anterior wall	7
Middle third	2			Posterior wall	3
Lower third	9			Lateral walls	3
		Apex	1		

Results

The results of treatment of patients with vaginal metastases from endometrial carcinoma may best be summed up by considering the survival rate. Of the 15 patients who had vaginal involvement at the time of diagnosis of endometrial carcinoma, or developed vaginal recurrences following treatment of the primary neoplasm, 1 patient was not accorded local therapy because of concurrent pulmonary metastases. The remaining 14 patients were treated with a variety of local radium techniques. Of the 14 thus treated, 13 patients failed to survive five years, while one patient is alive and well six years after therapy. The average length of survival after diagnosis of a secondary vaginal lesion was 14.2 months. The low five-year survival rate of 7 per cent in such patients is not a result of failure to control the isolated metastatic neoplasm. Seven of the 14 treated patients had no recurrence of the vaginal involvement after local treatment during follow-up periods that varied from 4 to 28 months. The poor prognosis in these patients with vaginal spread from endometrial carcinoma results from abdominal extension of the primary neoplasm or the appearance of other distant metastases. Two patients had metastases to the liver, 2 to the lung, 2 to bone, and 1 to cervical lymph nodes, all appearing after treatment of the primary carcinoma and the vaginal lesions.

Of 278 patients with endometrial carcinoma included in this study, 7 patients had vaginal metastases when first seen. No evidence of vaginal involvement was detected in the remaining 271 patients. Three patients were not accorded therapy for the primary neoplasm because of the presence of other

more acute diseases. Therefore, 268 patients who had no evidence of vaginal spread prior to therapy, were treated for endometrial carcinoma. In the 268 treated patients, there were 8 vaginal recurrences, a recurrence rate of 3.0 per cent.

The time lapse between the treatment of the primary carcinoma and the appearance of the vaginal recurrence varied between 2 and 92 months with an average time lapse of 23 months.

Relation of Vaginal Metastasis to Original Type of Therapy

The incidence of vaginal recurrence in relation to type of therapy given for the primary endometrial carcinoma is summarized in Tables III and IV. Each case is discussed in our Gynecology Tumor Conference, and the plan of therapy formulated for the individual patient is based on many factors. The advanced cases, of course, fall into the inoperable category. In these patients therapy consists primarily of irradiation. Such advanced cases are more prone to give rise to metastases; therefore one cannot compare the vaginal recurrence rate in patients treated solely by irradiation with recurrence rates for patients with earlier lesions for whom surgery or a combination of surgery and irradiation has been used. Since there has been no true control series in which surgical and radiological treatment have been alternated in patients with exactly similar stages of endometrial carcinoma, one may only compare the results in this series with grossly similar series reported elsewhere.

TABLE III. VAGINAL RECURRENCE OF ENDOMETRIAL CARCINOMA IN PATIENTS TREATED BY RADIOLOGICAL AND SURGICAL METHODS

TREATMENT	NUMBER	VAGINAL RECURRENCES
1. Irradiation Only.—		
a. External irradiation	6	0
b. External irradiation and radium	78	3
c. Radium	28	-1
2. Surgery Only.—		
a. Hysterectomy and removal of adnexa	16	1

TABLE IV. VAGINAL RECURRENCE OF ENDOMETRIAL CARCINOMA IN PATIENTS TREATED BY COMBINED RADIOLOGICAL AND SURGICAL METHODS

TREATMENT	NUMBER	VAGINAL RECURRENCES
1. External irradiation, radium, and hysterectomy	14	, 1
2. Preoperative external irradiation	14	1
and hysterectomy	103	1 .
3. Radium and hysterectomy	19	0
4. Hysterectomy and postoperative		
external irradiation	4	1

The 103 patients treated by preoperative external irradiation followed in approximately six weeks by total hysterectomy and removal of the adnexal structures demonstrated a vaginal recurrence rate of less than 1 per cent, for only 1 patient in this group developed a vaginal lesion. This very low recurrence rate is a substantial improvement over the vaginal recurrence rates reported by those employing total hysterectomy and bilateral salpingo-oophorectomy alone (Table V). Postoperative external irradiation used by Dobbie¹ was not successful in reducing the vaginal recurrence rate following surgical

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TABLE V. VAGINAL RECURRENCES OF ENDOMETRIAL CARCINOMA IN SURGICALLY TREATED PATIENTS

	NUMBER	RECURRENCES	PER CENT
Hysterectomy Only.—			
1. Ways	92	4	4.3
2. Dobbie ¹	64	7	11.0
3 Rickford ⁴	59	9	15.3
Hysterectomy and Postoperative Ex- ternal Irradiation.—			
1. Dobbie ¹	80	8	10.0
Preoperative External Irradiation and Hysterectomy.—			
1. University Hospital	103	1	1.0

Summary and Conclusions

Vaginal metastases and recurrences in patients with endometrial carcinoma seen at the University of Michigan Hospital from 1930 through 1949 are reported. The relation of vaginal lesions to the histological nature of the primary neoplasm is discussed and the exact site of the vaginal lesions reported. Vaginal recurrences after various types of therapy for primary endometrial carcinoma are reported. The following conclusions are drawn:

- 1. Adenocarcinomas with marked squamous metaplasia are more likely to give rise to vaginal metastases than are pure adenocarcinomas.
- 2. The lower anterior vaginal wall is the most frequent site of vaginal spread from endometrial carcinoma.
- 3. The prognosis of patients with vaginal involvement from endometrial carcinoma is poor.
- 4. The number of vaginal recurrences of endometrial carcinoma can be definitely reduced if preoperative external irradiation is used in surgically treated patients.

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CARCINOMA OF THE CERVIX ASSOCIATED WITH PREGNANCY

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THE recent interest in cervical carcinoma with coexistent pregnancy is evident from the multiplicity of reports concerning this problem and concerns particularly the status of precancerous lesions of the cervix during pregnancy. It is recognized that early cervical malignancy, especially in pregnancy, offers a challenge to the pathologist's experience. The many comprehensive studies of the pregnant cervix¹⁻⁶ stressed that the histopathological alterations which occurred were deviations clearly in the direction of hyperactivity, but that these same changes tended to regress rapidly following parturition. The available evidence was not sufficiently conclusive, and it could not be assumed that the changes, such as cellular hyperactivity, hyperchromatism, and increased mitotic figures through the full thickness of the epithelium, which in the nonpregnant cervix would indicate carcinoma in situ, had the same significance in the case of the pregnant cervix.

Therefore, we reviewed the cases of carcinoma, invasive and noninvasive, of the cervix coincidental with pregnancy. From the cancer file there were 19 cases of substantiated carcinoma in situ of the cervix, and careful investigation did not reveal any case associated with a gestation. All of the 12 established cases of cervical malignancy associated with pregnancy were the overt invasive type of carcinoma. Over the years 1931 to 1954 biopsies were made on more than 3,916 cervical lesions; in the majority of instances this was done in the hospital, where more facilities were available in the event of hemorrhage or for a lesion requiring treatment. There had been no reluctance by the members of the staff to take biopsy specimens from a cervix in the presence of a gestation, and over 170 cervical lesions were investigated during pregnancy. In addition, since 1946 over 200 cesarean section—total hysterectomies were performed and cervical specimens were prepared in each case. For some years, as a supplementary diagnostic aid, Papanicolaou smears were made on suspicious cervical lesions and routinely on patients over 35 years of age. Regardless of the rarity of the occurrence of cervical neoplasm during pregnancy, any investigation of bleeding during pregnancy must eliminate the possibility of such a lesion.

From 1931 to 1954 there were over 81,806 obstetric patients at the Chicago Lying-in Hospital; cervical carcinoma coexisting with the pregnancy was diagnosed in only 12 cases, an incidence of one in every 6,817 women, or 0.014 per cent. In comparison with the reported incidence at other institutions, as summarized in Table I, our incidence was slightly lower than the general

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average of the entire group. Probably even more significant was the observation that, despite the fact that an additional 42,087 obstetrical patients had been admitted over an eight-year period, there had been no appreciable alteration in incidence since the previous review by Willson¹³ in 1945, who presented 6 cases that occurred among 39,719 patients from 1931 to 1945.

TABLE I. FREQUENCY OF CERVICAL CARCINOMA COMPLICATING PREGNANCY

		TOTAL NO. OF PREG-	CERVICAL	CARCINOMAS
AUTHOR	HOSPITAL	NANCIES	NO.	1 %
Hirst ⁷	Philadelphia Lying-In Hospital	46,806	. 5	0.010
Danforth ⁸	Evanston Hospital	20,444	3	0.014
Johnson and Weinfurtne	er9 Louisville General Hespital	29,394	12	0.040
	, University of Virginia	8,450	5	0.059
Ward ¹¹	Woman's, N. Y. C.	36,274	10	0.027
Eastman ¹²	New York Hospital	41,451	3	0.007
This report, 1931-1953	Chicago Lying-in	81,806	12	0.014
Average				0.024

Of the uterine malignancies treated at this hospital, 485, or 69 per cent, were cervical carcinoma and the incidence of pregnancy in carcinoma of the cervix was 2.5 per cent, which represented a slightly higher rate than the reported frequencies or general average (1.9 per cent) at the other institutions as summarized in Table II. All the patients in this series were white. The youngest was 27 and the oldest was 46 years of age. The average age was 35.2 years. The average duration of and age at marriage was 15.2 years and 20.8 years, respectively. The number of pregnancies ranged from 2 to 14. The average gravidity was 7.6 and parity was 5.5. The results closely paralleled the observation of Meigs, to who emphasized the tendency of patients who were found to have cervical carcinoma to have married younger and to have had a higher frequency of children.

TABLE II. INCIDENCE OF PREGNANCY IN CARCINOMA OF THE CERVIX

	,	CERVICAL CARCINOMA	IN PREG	NANCIES
AUTHOR	SOURCE	NO.	NO.	1 %
Sadugor, Palmer, and Reinhard ¹⁴	Rosewell Park Memorial Institution	4,652	124	2.66
Johnson and Weinfurtner ⁹	Louisville General Hospital	778	12	1.54
Thornton, Nokes, Wilson, and Brown ¹⁰	University of Virginia Hospital	280	5	1.7
Hirst ⁷	Philadelphia Lying-In Hospital	905	18	1.9
Maino and Mussey ¹⁵	Mayo Clinic	3,570	26	0.70
This report, 1931 to 1953	Chicago Lying-in Hospital	485	12	2.47
Total		10,670	197	
Average				1.82

The symptoms of cervical carcinoma with coexistent pregnancy followed closely the expected pattern of cervical malignancies plus the symptoms of pregnancy. Regardless of the source, all the authors⁷⁻¹² agreed that vaginal bleeding was the most frequent initial complaint. In 11 of our 12 patients, or

91.6 per cent, vaginal bleeding was the initial complaint and the presence of the pregnancy tended to obscure and mask the diagnosis. In the remaining case the presenting complaint was profuse foul vaginal discharge during the immediate six-week postpartum period. No characteristic type of bleeding could be detected except that it was always painless. An attempt was made to correlate the duration of the complaints with the type, grade, or clinical stage of the lesion, but no significant correlation could be made.

In every instance the initial diagnosis was established by a biopsy. Squamous-cell carcinoma was found in 10, or 83.4 per cent, of the lesions, and the remaining 2 lesions, 16.6 per cent were adenocarcinomas. No correlation could be noted between the grade and the clinical stage or between grade and five-year survivals. Our finding closely paralleled similar observations by Maino, Broders, and Mussey¹⁸ in their evaluation of the pathology in 26 cases of cervical neoplasms coincidental with pregnancy. Clinically, the carcinomas of the cervix were evaluated according to the League of Nations Classification as follows (Table III): 3 cases, or 25 per cent, in Stage I; 7 cases, or 58.4 per cent, in Stage II; and 2 cases, or 16.6 per cent, in Stage III. None of the cases in this series had advanced to Stage IV. In a comparison of the relation of the carcinoma to parturition, 7 cases were diagnosed in the antepartum period or at delivery, and in the remaining 5 cases the diagnosis was made between the sixth and thirteenth postpartum weeks, or an average of 9.6 weeks after delivery. Clinically, the neoplastic process in the postpartum group was far more advanced, for both of the Stage III cases and 3 of the Stage II cases were in this group. The average duration of symptoms, however, was essentially the same for both groups. A definite relationship was noted between the increasing duration of the gestation and the clinical stage of the lesion at the time of diagnosis. The trend indicated that the more advanced stages of the carcinoma directly paralleled the advancing duration of the pregnancy.

TABLE III. EXTENT OF MALIGNANCY IN RELATION TO FIVE-YEAR SURVIVAL

	STAGE I	STAGE II	STAGE III
Number of cases	3	7	2
Percentage of all cases	25	58.3	16.6
Percentage of five-year survival	100	42.8	0.00
Percentage of all five-year survival	50	50	0.00

Fetal Prognosis and Effect of Carcinoma on the Pregnancy

The influence of the cervical carcinoma on the fetal survival in this series was not appreciable. In one instance, the diagnosis of carcinoma was established in a 12 to 14 weeks' gestation and this pregnancy was terminated by a subtotal hysterectomy following radium therapy. Among the eleven remaining viable gestations, one fetal death resulted and can be directly attributed to the presence of the carcinoma. In this instance a term 3,200 gram stillborn infant that died intrapartum resulted from a seven-day prolonged labor in the home, which was finally terminated by a spontaneous delivery by a home maternity service. The six week post partum examination in this patient revealed a Stage III cervical carcinoma. The relative fetal mortality for the series was 9 per cent and the average duration of gestation was 36.4 weeks.

In 5 cases, one of which was later determined not to be carcinoma (Table IV) antepartum radium therapy was administered in therapeutic dosage with an average of 3,815 mg./hr. between the thirtieth and thirty-second weeks of the gestations. The average time interval between therapy and delivery

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was 26.0 days with a range of 12 to 42 days. As regards the position of the fetus during therapy, 4 were cephalic and the remaining was a single breech. Only one of the 5 infants showed any evidence of radiation trauma and this was characterized by two small bald areas of the right parietal region which corresponded to the position at delivery. Follow-up examinations at 6 months or more were available in 4 of the infants, but for one only an examination at 6 weeks was obtained. All were noted to have progressed normally in development and growth. One of the 4 infants died at 9 months, however, from a cause entirely unrelated to the radiation therapy, namely, an intussusception with gangrene of a Meckel's diverticulum and peritonitis. Unfortunately, the head examination was disregarded.

There were 7 vaginal deliveries and 4 cesarean sections among the 11 viable gestations. Four of the 7 patients who delivered vaginally progressed normally and uneventfully, but the remaining 3 cases were complicated. There were 2 cases of prolonged labor, one of 52 hours and the second of seven days which resulted in the stillbirth, but both of these cases were terminated by spontaneous deliveries. In the third case, placenta previa lateralis was incorrectly diagnosed and induction by rupture of the membranes and the use of a Voorhees bag was successfully performed at 34 weeks.

In the group of 4 patients who received antepartum radium therapy, 3 were delivered abdominally, but only one of the 3 sections was nonelective due to cervical dystocia with a 19 hour test of labor. The fourth patient who received antepartum radium delivered spontaneously a single breech after a one-hour labor. In the series one additional elective cesarean section was performed for the purpose of combining the section with radical surgery.

Since all the patients were multiparous with normal obstetrical histories, directly, or indirectly, the indications for all 4 sections can be attributed to the carcinoma. In addition, the 2 cases of prolonged labor were directly related to the presence of the cervical lesions. Interestingly, the complicated cases, namely, the prolonged labor cases and the placenta previa lateralis, resulted in a poorer prognosis and no five-year survivals were found in this group. There was no significant difference in the five-year survival rate between the vaginal and abdominal deliveries.

Definitive Treatment and Prognosis

For many years now, the accepted program at this hospital has been for each obstetrical patient to receive two or more examinations and visualizations of the cervix by a competent clinician during the prenatal course, which usually involves a five- to seven-month period. Epperson and co-workers have stressed the low incidence of even minor complications associated with cervical biopsies. In this series there is wide distribution of clinical stages, despite the relatively close supervision during the prenatal period, and even the more advanced stages are found. This would tend to reflect the need for greater diagnostic awareness and more intensive investigation of bleeding irrespective of the presence of a pregnancy. This series all too well demonstrates the value of early diagnosis in terms of clinical stage, since the stage was the most significant criterion of prognosis and response to treatment.

In Table V, the five-year survivals were correlated with stage and therapy. The attempt to evaluate treatment more adequately in these cases was prepared with full recognition of the risk involved and of the complete lack of statistical significance. As in uncomplicated cervical carcinoma, Stage I cases uniformly responded well, since 100 per cent five-year survivals were obtained. But the results diminished rapidly in the more advanced lesions, as demonstrated by Stage III cases in which there were no five-year survival

TABLE IV. RESULTS OF ANTEPARTUM RADIUM TREATMENT

PATIENT AND UNIT NO.	LENGTH OF GESTATION AND STAGE OF CA.	RADIUM, DATE	INTERVAL TO DELIVERY DAYS	TO DELIVERY DELIVERY DATE AND TYPE DAYS OF LABOR	POSITION, SEX, WEIGHT, FOLLOW-UP, AND FETAL SURVIVAL	ADDITIONAL TREATMENT	SURVIVAL IN YEARS
N. W. 326686	32 weeks Stage II	2/9/44 3,446 mg. H tandem* needles	00 60	3/20/44 No labor Section and subtotal hysterectomy and radical surgery	ROT, male, 2,675 grams Living and well 6 weeks	Radium	1½. Died Oct. 8, 1945, carcinomatosis
V. G. 188041	32 weeks Stage I	12/1/37 3,000 mg. H* cap- sule (50's)	12	12/13/37 No labor Section and radical surgety	LOT, male, 2,295 grams Bald spots Living and well 9 months	X-ray	16½. Living. No recurrence
J. C. 432537	33 weeks Stage II	7/14/51 5,690 mg. H colpostat tandem*	55	8/5/51 19 hours Cervical dystocia Section and radical surgery	ROT, male, 3,160 grams Living and well 6 months Erythroblastosis	None	2½. Living. No recurrence
A. L. 63977	30 weeks Stage II	8/4/32 3,100 mg. H tandem* colpostat	18	8/22/32 One hour Spontaneous Single breech	LST, female 2,020 grams X-ray Living and well 6 months	X-ray	7½. Died Feb. 11, 1940, carcinomatosis
C. S. 54748	30 weeks Stage I	2/11/32 3,800 mg. H tandem* colpostat	42	3/26/32 No labor Section and radical surgery	LOT, male, 3,235 grams Living and well 1953	Reviewed; not carci- noma	22½. Living. No recurrence. Living and well

*Tandem or capsule held in place by a suture through cervix.

cases. The use of antepartum radium offered the same absolute survival rate as prevailed in the series, or 50 per cent. In this series no detailed elaboration of therapy programs or alternatives for the first and second trimesters of the pregnancy was considered, since 11 of the 12 patients were in the third trimester. Briefly, our method is to destroy the lesion by combining the maximal irradiation to the cervix, and/or the radical pelvic surgery, regardless of fetal status. In the 4 patients who underwent combined radical surgery, only one complication resulted, namely, ligation of both ureters with subsequent transplantation of one to the skin and of the other to the bladder.

TABLE V. TREATMENT IN RELATION TO STAGE

	1						5	-YEAR	SURVI	VAL
			ST	AGE			NO.	OF		
TREATMENT		I	1	11	I	П	CA	SES	9	%
Radium and x-ray	1		4		2		7		58.3	
Number of five-year survivals		1		2	0.			3		42.8
Radium, x-ray, and surgery	2		2		0		4		33.3	
Number of five-year survivals		2		1		0		3		75
Radium and surgery	0		1		0		1		8.3	
0 0		0		0		0		0		0

If a uniformity of pattern of treatment were to be evolved from our evaluation of the 11 cases seen in the last trimester, the following program would be the method of choice without a detailed exploration of the more remote possibilities.

1. Abdominal delivery would undoubtedly be the method of choice, and fetal survival would be determined by the stage of viability at the time of diagnosis, but two to three weeks' delay would be justifiable.

2. Intensive radium therapy to the cervix, and in three to four weeks, depending on the period of gestation, cesarean section combined with the most extensive radical pelvic surgery in Stage I and the majority of Stage II cases.

3. In the more advanced stages or in poor surgical risk patients, radium therapy, and delivery by cesarean section with subtotal hysterectomy, followed by deep x-ray therapy and more radium to the cervix.

The clinical stage remained the single constant and most important factor in predicting the survival rate, as clearly shown in Table III. The pattern of the malignant process was comparable in all aspects to that of the usual uncomplicated cervical carcinoma. The absolute five-year survival rate was 50 per cent and the ten-year survival rate was 25 per cent. The survival rates were essentially unaltered by the associated pregnancy. Others, such as Sadugor, Palmer, and Reinhard, in a survey of 126 cases, demonstrated no unfavorable effect on the carcinoma survival results by the presence of a gestation. In 11 of the 12 cases follow-up of five or more years was available and the relative five-year survival rate was 54.6 per cent, which compared favorably with that in other similar series.

Comment

Whenever there is possibility of error in microscopic diagnosis, the sections should be re-evaluated by several competent gynecological pathologists, or the patient should be carefully observed and repeat cervical biopsies performed.

The following 3 cases, one observed and 2 treated, illustrate the need for extreme caution in diagnosis in the presence of a gestation:

CASE 1.—T. T. (No. 201017), a 33-year-old gravida i, para 0, was first seen on July 8, 1938, and examination showed a cervix which was described as showing "decidual reaction." On Oct. 21, 1938, slight vaginal bleeding occurred, and a benign cervical polyp was removed. No further bleeding occurred until Feb. 8, 1939, at which time the patient was 41 weeks pregnant. Examination disclosed a friable everted lesion of the cervix which grossly suggested malignancy. Because of severe preeclampsia and possible malignancy, the pregnancy was terminated on Feb. 10, 1939, by laparotrachelotomy, which was preceded by a cervical biopsy. The tissue removed was reported as probably adenocarcinoma. After review of the section (Fig. 1), however, it was decided that the lesion was benign. Without treatment the cervix healed and remained normal. In 1947, a repeat biopsy was performed and no evidence of malignancy was found. Had not the original section been carefully re-evaluated, this patient would undoubtedly have been subjected to radiation therapy with castration and possible trauma to normal structures.

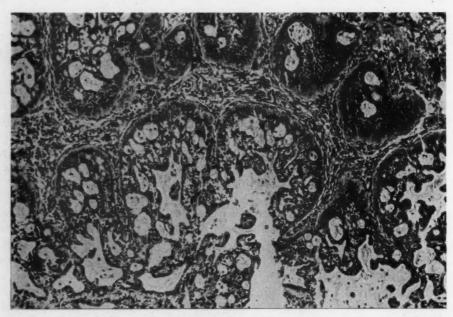


Fig. 1.—Case 1. The lesion was initially considered to be probable adenocarcinoma, but on re-evaluation was considered benign.

CASE 2.—C. S. (No. 54748), a 24-year-old gravida ii, para i, was first seen in the clinic in February, 1932, at 30 weeks. At that examination there was noted an eversion of the cervix and papillary outgrowths (Fig. 2) on both lips. Because of a pathological diagnosis of adenocarcinoma of the cervix, a plaque containing 200 mg. of radium was applied to the cervix for a total dosage of 3,800 mg. hr. Seven weeks later a cesarean section and modified Wertheim hysterectomy were performed. Later, several gynecological pathologists were all of the opinion that the lesion was not malignant.

Later the patient developed proctitis, which necessitated biopsy and treatment, and resulted in severe pelvic pains. Although the patient was alive and well in June, 1953, she had been subjected to radium therapy and an extensive operative procedure for the treatment of a benign cervical lesion.

CASE 3.—Mrs. X. (from outside institution), a para iii, gravida iv, aged 33 years, whose last menstrual period was March 26, 1945, and whose estimated date of confinement

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3, 1e was Jan. 4, 1946, was found to have a cervical lesion during her routine prenatal examination. Her prenatal course had been uneventful. She was referred to a consultant obstetricin who also thought the lesion was suspicious and performed a biopsy. The original pathological diagnosis (Fig. 3) was: "Small epidermoid carcinoma of the cervix uteri, Grade III cellular malignancy." Deep x-ray therapy was instituted. Because there was some doubt in the opinion of the consultant, further sections were made and these were reviewed by three gynecological pathologists who agreed that the tissue represented a marked decidual reaction of the cervix and no malignancy was present. The deep x-ray

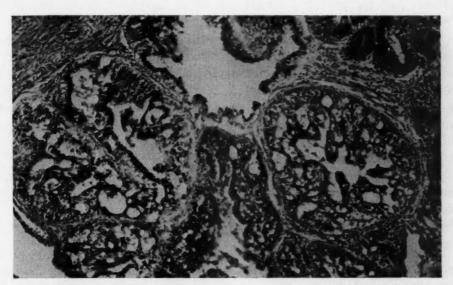


Fig. 2.—Case 2. Section from cervix. The patient was treated with radium and cesarean section and modified Wertheim hysterectomy because of an initial diagnosis of a malignant process which was later reviewed and considered benign.

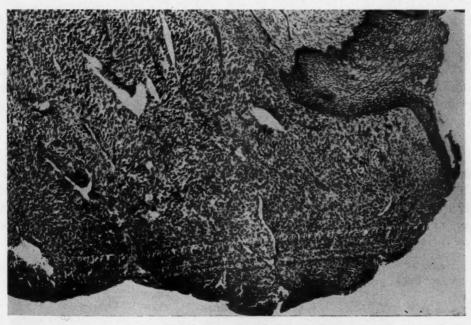


Fig. 3.—Case 3. This lesion was originally considered "small epidermoid carcinoma of the cervix."

therapy was stopped immediately but she had already received treatments for three weeks. On Aug. 26, 1945, a hysterectomy was performed and a macerated fetus was delivered. A follow-up examination on Nov. 4, 1945, showed the cervix to be normal. She was known to be living and well in October, 1953; however, she is incapable of further pregnancies.

In the current literature the pathological diagnosis of carcinoma in situ has assumed proportions in keeping with the needed enthusiasm for early diagnosis, but its probable actual incidence has been overestimated. one denies that the condition exists as a pathological entity. One must concede, however, that its exact status is still undetermined, especially in the presence of the cervical changes associated with pregnancy. Novak and Galvin¹⁹ have reviewed 25 cases of noninvasive carcinoma of which 23 have been incorrectly diagnosed. Complete regression of the lesions has been described by numerous authors^{6, 20-24} who have followed cases which have been diagnosed by biopsy during pregnancy and in which no evidence of carcinoma could be detected after parturition. Our findings do not substantiate any high incidence during pregnancy as reported in the current literature.24-27 Our incidence of carcinoma in situ, 3.9 per cent of all cases of cervical carcinoma, approximates the incidence of 2.6 per cent reported by Piper²⁸ in the Mayo Clinic series.

Summary

Twelve cases of cervical carcinoma associated with pregnancy, an incidence of 0.014 per cent, are presented with observations concerning the clinical aspects and treatment. The five-year survival rate in this series is 50 per cent.

Direct visualization of the cervix and, when it is indicated, biopsy in the hospital are the important steps in the routine prenatal examination and in the investigation of bleeding during any trimester of pregnancy. The need for study by a competent pathologist and caution in the evaluation of cervical lesions during pregnancy, especially carcinoma in situ, are stressed.

The clinical stage remains the single most important prognostic criterion. No unfavorable influence by the pregnancy could be demonstrated, since survival results and clinical aspects of the 12 cases are similar to those in uncomplicated cervical carcinomas. Fetal mortality is only slightly increased.

In Stage I or II cases, the method of choice is cesarean section followed by the Wertheim type hysterectomy and lymphadenectomy. If there is extensive involvement of the cervix, radium is inserted into the cervical canal and retained by a suture for a dose of 4,000 mg./hr., and is followed by cesarean section with radical surgery, or, if the parametrial tissues are involved, with subtotal hysterectomy, so that 3 to 4 cm. of cervix are left for further radium therapy and deep x-ray therapy to the parametria.

I wish to express my appreciation to Dr. William J. Dieckmann for his interest and suggestions in the preparation of this paper.

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CORDOTOMY FOR RELIEF OF PAIN IN INCURABLE SQUAMOUS-CELL CARCINOMA OF THE CERVIX UTERI*

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A SIGNIFICANT proportion of patients who, for one reason or another, are not cured by treatment of a cervical carcinoma present a major problem of pain control. If this be severe or if there be a reasonable prospect that it will last for an appreciable period of time, something more than the use of narcotics is desirable. It is a great relief to all concerned when the pain is removed and the patient left in a condition which will allow her to return to something approximating her normal activities for the relatively short time which remains.

Spinothalamic tractotomy is the most efficient measure for the relief of intractable pain of incurable carcinoma of the cervix. The fact that pain from carcinoma of the cervix is almost invariably below the upper thoracic segments makes it especially susceptible to relief by spinothalamic tractotomy.

Forty patients with pain secondary to incurable carcinoma of the cervix were subjected to spinothalamic tractotomy on the Neurosurgical Service of the University Hospitals between Jan. 1, 1937, and Dec. 31, 1954.

Indications for tractotomy are: (1) severe intractable pain; (2) an incurable lesion, proved or suspected; (3) a life expectancy of at least three months.

When patients begin to depend on narcotics for the relief of pain, tractotomy should be considered and it should be performed before they develop an increased tolerance to narcotics or become addicted. The examination preliminary to spinothalamic tractotomy in these 40 patients consisted of physical examination, roentgenological examination of the chest and pelvis, and, when indicated, cystoscopy with pyelography, proctoscopy, spinogram, and psychiatric evaluation. Through this examination, evidence of progressive carcinoma was found in 36, but in the other 4 cases no evidence of persistent or recurrent cancer or other organic cause of pain was demonstrated.

The patients varied in age from 25 to 69 years. Five were less than 35 years old. The median age was 47 years. At the time definitive treatment for cancer was begun, the League of Nations Classification was I in 5, II in 14, III in 10, IV in 1, and clinical staging was not applicable in 10, most often because they had been previously treated elsewhere.

The primary treatment for the malignant lesion was high-voltage x-ray therapy and radium in 36. It was surgical in 4. Eleven of those who received

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irradiation therapy and all those who were treated by surgery had their primary treatment elsewhere. Of the 36 treated by irradiation, 16 had had a second course of irradiation therapy.

Usually the pain was dull and intermittent but progressed to become widespread or diffuse, sharp, severe, and constant. The initial site was the anterior thigh in 9, the hip region in 7, low back in 6, the leg in 5, the lower abdomen in 4, the perineum in 3, the rectum in 2, the groin in 3, the sacral region in 1, and the posterior thigh in 1. Pain began in most of these women between 9 and 15 months (mean $11\frac{1}{2}$ months) after therapy for carcinoma was instituted but the range was wide, varying from 7 to 156 months.

Most of these patients had pain for 4 to 8 months (mean 6¾ months) before they were referred to neurosurgery for tractotomy but this interval varied from 3 weeks to 3 years.

Spinothalamic Tractotomy

The transmitting fibers of pain sense enter the cord through the dorsal root and terminate on cells in the dorsal horn of gray matter. These dorsal horn cells give rise to fibers which cross over to the opposite side of the cord through the ventral white commissure to enter the lateral spinothalamic tract in which they ascend to the ventral nucleus of the thalamus. The fibers subserving temperature sense have the same course and are intimately associated with those for pain. Therefore, when the lateral spinothalamic tract is cut, both pain and thermal sensation are abolished in the more caudad segments of the opposite side. Since this pain pathway ascends a few segments in the spinal cord before crossing over to the spinothalamic tract of the opposite side, the level of analgesia which follows a cordotomy is always at least a few segments lower than the cut in the cord. Spinothalamic cordotomies are never done below the upper thoracic segments. High cervical cordotomy made at approximately the second cervical segment gives best results. At this level the spinothalamic tract appears to be more constant in its position so that with high cervical cordotomy it is most certain that the entire lateral spinothalamic tract has been cut. This gives a high level of analgesia, usually up to the fourth cervical segment. There are not areas of sparing, and this level is more likely to remain fixed without later drop below the site of pain. Therefore, it is customary now at the University of Minnesota to carry out high cervical cordotomy instead of high thoracic, even though the pain for which the cordotomy is done is lower abdominal, pelvic, or lower extremity.

In these 40 patients, a total of 46 operations were done and 66 incisions were made in the cord. A second operation was performed in 3 patients and the cordotomy incision repeated because the first had not produced a high level of analgesia. Three patients who originally had a unilateral cordotomy subsequently had cordotomy performed for pain that developed on the opposite side. Nine of the cord incisions were high cervical spinothalamic tractotomies.

Results

Thirty (75 per cent) of the 40 patients had complete relief of pain on discharge from the hospital, 6 experienced moderate relief, 3 poor or no relief, and one died.

High cervical and high thoracic cordotomies were done as either unilateral or bilateral operations. Four unilateral high cervical cordotomies were done with complete relief but 3 patients later developed pain on the opposite side. One of these then had a high contralateral thoracic cordotomy and again had complete relief. Sixteen had a unilateral high thoracic cordotomy with com-

plete relief in 11, moderate relief in 3, and poor relief in 2. Five later developed pain on the other side. In one of these 16 cases the spinothalamic tract was apparently uncrossed. Section of the spinothalamic tract produced analysesia and thermanesthesia only on the side of cordotomy and when a later cordotomy was done on the side of the pain, complete relief was obtained with analysesia and thermanesthesia again on this side. This unique case has been reported in detail elsewhere. In 3, a sufficiently high level either was not obtained to relieve the pain or later dropped with return of pain. In some of these and also some of those who developed pain on the opposite side, complete relief was ultimately obtained by additional cordotomies. Bilateral high thoracic cordotomy was done on 16 with complete relief in 12, moderate in 3, and no relief in one.

High bilateral cervical cordotomy was done in one case with immediate death. This operation was done with the patient in the sitting posture and death was due to a sudden and severe drop in blood pressure when the second side of the cord was incised. Additional experience has demonstrated that this severe drop in blood pressure invariably occurs when a bilateral cordotomy is done with the patient in the sitting posture and hence all bilateral spinothalamic tractotomies should be done in the prone position. The average survival after cordotomy for 34 patients now dead was 5.7 months.

Conclusions

Anterolateral spinothalamic tractotomy should be offered to patients suffering intractable pain from incurable carcinoma of the cervix. High cervical cordotomy for relief on the side with most severe pain combined with a high thoracic cordotomy on the opposite side is the most satisfactory type of cordotomy. If unilateral cordotomy is done for what is apparently unilateral pain, many, if not most, of these women will then complain of pain on the opposite side or will later develop pain on the opposite side.

In general, the results of cordotomy in these 40 women were very gratifying; 75 per cent were completely relieved of pain when they left the hospital.

The incidence of persistent urinary retention, the most dreaded complication of cordotomy, was low. It occurred in only 2 women who had normal bladder function before spinothalamic tractotomy.

Summary

Anterolateral spinothalamic tractotomy has been performed on 40 patients at the University of Minnesota Hospitals since Jan. 1, 1937, for relief of pain due to hopeless recurrent carcinoma of the cervix. Some of the clinical features of these cases are reviewed.

It has proved to be remarkably effective in the relief of intractable pain. Undesirable side effects and, in particular, loss of urinary control were rarely produced.

It is the method of choice in the therapy of intractable pain in recurrent or untreatable carcinoma of the cervix.

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THE POTENTIALITIES OF THE SMEAR TECHNIQUE FOR THE DIFFERENTIATION OF NONINVASIVE AND INVASIVE CERVICAL CARCINOMA*†

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THE differential diagnosis between an invasive and a noninvasive cancer by means of cytological smears has attained little clinical use. Since the cytologist customarily does not and should not distinguish between malignant and benign, but only between normal or abnormal, we must realize that it does not fall within his scope to demonstrate definite evidence of malignancy, or even the extent of a malignant lesion. This becomes particularly clear when we realize that while all cancers must exfoliate abnormal cells, all exfoliated dyskaryotic or abnormal cells do not necessarily derive from a cancer.

Under the present accepted hypothesis definitions of invasive and non-invasive squamous-cell careinoma are as follows:

A squamous-cell carcinoma is a mass of atypical squamous epithelial tissue with excessive growth of an autochthonous type, persisting in the same excessive manner after cessation of the stimulation which provoked the epithelial change. In the behavioristic classification the term carcinoma refers to a clinically malignant lesion, which in the untreated patient implies a poor prognosis.

A noninvasive squamous-cell carcinoma is an atypical squamous epithelial tissue which persists after the cessation of the stimulation which provoked the epithelial change; it can potentially have excessive growth of the autochthonous type. A noninvasive carcinoma (carcinoma in situ, preinvasive, intraepithelial, or surface cancer) is an *irreversible* epithelial atypia showing histological, histochemical, cytological, and biochemical characteristics or anomalies qualitatively and quantitatively identical with those of an invasive carcinoma except for the invasion of the epithelial cells into the connective tissue. A noninvasive carcinoma belongs, under the behavioristic classification, to the clinically malignant tumors as it has the potential of becoming an invasive carcinoma either in a very short time or after a latent period of many years.

Reversible atypical (carcinomimetic) epithelial lesions—even if they cannot be definitely distinguished with our present microscopic methods—should not be called "cancer." Regression of these atypical epithelial lesions can be observed after the cessation of the stimuli which provoked the change, e.g., after elimination of local irritation (healing erosion, Trichomonas vaginitis) or after terminaton of pregnancy.

†Presented at a meeting of the Chicago Gynecological Society, March 18, 1955.

^{*}Supported by an Institutional Grant of the American Cancer Society and the Goldblatt Cancer Research Grant.

Because carcinomimetic, dysplastic lesions cannot always be distinguished from carcinoma in situ in the histological sections, it would be logical to introduce another term for these borderline cases which is not directly associated with a clinical prognosis. Held²³ recommended naming these lesions "atypical epithelium without invasion." The use of this terminology would leave the decision up to the clinician.

There is no agreement among authors as to whether or not a cytological differentiation of the extent of a malignant lesion can be or should be attempted. The diagnosis of the extent of a lesion and the definitive diagnosis of malignancy are up to the pathologist. There is evidence enough to say a differentiation by means of the cytological smear is possible with some degree of accuracy. Though differential analysis by means of cytological smears may have limited practical value, it is of definite scientific interest.

Over- or underestimation of any clinical technique may endanger the welfare of our patients. The diagnostic accuracy of cytological analysis of smears is, like almost all clinical diagnostic procedures, largely dependent upon experience. I have personally made cytological examinations on more than 25,000 patients (with approximately 75,000 specimens). This number does not include smears eliminated by prescreening personnel. In the differentiation between invasive and noninvasive carcinoma by cytological means, there is a distinct danger of overreaching the reasonable limits of the methods. Nevertheless, we are now convinced that exfoliative cytology has a distinct role in cancer screening (and, in addition, in the evaluation of hormonal effects).

A vaginal, a cervical, and an endocervical smear is prepared from every patient, a complete cytological description is made on every case as described previously.⁵⁷ Through such a description an evaluation of the amount, the localization, and the degree of degeneration of leukocytes and erythrocytes, and a rough, but clinically useful bacteriological classification are given. The squamous epithelial cells, and their degree of cornification are described and an estimate of the relationship of folded to flat cells, and of crowded to singly lying cells is given. This in addition permits a clinically useful hormonal evaluation of the smears.

The differentiation of invasive and noninvasive cancer by means of smears is based, in my opinion, on several, but nonspecific, criteria, most of them dealing either with a quantitative study of the epithelial cells or with the surroundings of the epithelial cells. Cytometry is put aside here because it is the purpose of this paper to discuss the possibility of differentiating the invasive and noninvasive lesions by means of the routine cytological smear examination alone, and not to involve time-consuming methods which would require special equipment.

Differentiation of Invasive and Noninvasive Cancer

1. Evaluation of the Surroundings of the Cells (Table I).—A smear from an invasive cancer will never show a completely healthy vaginal flora with Bacillus vaginalis Döderlein and bacterial cytolysis.⁵⁴

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TABLE I. SURROUNDINGS

	DYSPLASIA	CARCINOMA IN SITU	INVASIVE CARCINOMA
Vaginal flora	Can be healthy (Döderlein bacillus)	Can be healthy (Döderlein bacillus)	Never completely healthy, never bacterial cytolysis
Leukocytes in fornix vaginae	None, or few well- preserved	None, or few well- preserved	Always many and mostly degenerated
Red blood cells in fornix vaginae	None (usually)	None (usually)	Mostly present

An invasive cancer is more likely to bleed, and to show more leukocytes in the smears than a noninvasive lesion.

2. Approximative Relationship of Normal, Dyskaryotic, and Abnormal Cells (Fig. 1).—The differentiation may be aided by a study of the relationship of normal to dyskaryotic cells, and of dyskaryotic to abnormal cells (if we use this term in referring to a "cancer type" cell). The largest absolute number of exfoliated, mostly well-preserved, dyskaryotic cells is seen in noninvasive carcinoma. Their presence is probably due to a lack of sufficient local nourishment.

APPROX. RELATION OF NORMAL TO DYSKARYOTIC CELLS

	DYSPLASIA	CA IN SITU	INVASIVE CA
O O O	100	100	100
DYSKARYOTIC	5	40	10

APPROX RELATION OF DYSKARYOTIC TO ABNORMAL CELLS

	DYSPLASIA	CAINSITU	INVASIVE CA	
DYSKARYOTIC	100	100	100	
ABNORMAL	0	40	200	

Fig. 1.

The quantitative relationship is highly variable in some cases. This becomes particularly clear when we realize that most of the early invasive lesions have more or less extensive noninvasive carcinomatous borders, and that noninvasive cancers can on the other hand have more or less dysplastic borders.

3. Locality of the Dyskaryotic and Abnormal Cells (Fig. 2).—It is of some further diagnostic value to differentiate the locality of the dyskaryotic or abnormal cells. In Chicago Lying-in Hospital, a vaginal, a cervical, and an endocervical smear is prepared from every patient.⁵⁷ A noninvasive cancer, it has been found, apparently due to its site of origin, will exfoliate most of its atypical cells into the endocervix, while the invasive cancer shows a marked exfoliation into the fornix vaginae. Most of the abnormal cells found in the endocervical smears of patients with invasive cancer will show more degenerative cell changes than the abnormal endocervical cells exfoliated from noninvasive lesion.

4. Qualitative Differences of the Dyskaryotic or Abnormal Cells (Fig. 3).—
There are no known qualitative epithelial cell criteria that might be considered "specific." We have seen small invasive cancers which have exfoliated only dyskaryotic cells, to the exclusion of all other types. We have a few noninvasive cancers which have exfoliated the type of cells we would expect to see in an extensive, highly active invasive cancer.

DYSKARYOTIC AND ABNORMAL CELLS FOUND IN VAGINAL CERVICAL OR ENDOCERVICAL SMEARS

- V	DYSPLASIA		CA IN SITU		INVASIVE CA	
	DYSKAR.	ABNORM.	DYSKAR.	ABNORM.	DYSKAR.	ABNORM.
115	++	-+	-+	-+	+	++
CENY	++	-+	++	+	+++	+++
ENDO	-+	0	+++ (WELL-PR	+ RESERVED)	+ (DEGEN	ERATED)

Fig. 2.—In dysplasia most of the atypical cells are found in vaginal or cervical smears. In carcinoma in situ most of the dyskaryotic and abnormal cells are found in the endocervical smears; these cells are mostly well preserved. In an invasive cancer most of the dyskaryotic and abnormal cells are found in the cervical smears. The abnormal cells found in the endocervix are mostly degenerated.

DYCKADYOTIC AND A PHOPMAL SOLIAMOLIS EPITHELIAL CELLS

AVEN ABNATIA	ABMODIAN	DYSPLASIA		CA IN SITU		INVASIVE CA	
DYSKARYOTIC	ABNORMAL	DYSKAR.	ABNORM.	DYSKAR.	ABNORM.	DYSKAR.	ABNORM.
HYPERTROPH DEEP	SPINDLE SHAPED	+++	0	-+	+	•	+
DYSKAR. SUPERF.	TADPOLE	**	•	+	-+	-+	++
DYSKAR. INTERM.	MULTI- NUCLEATED	+	0	++	-+	-+	++
DYSKAR. PARABASAL	MACRONUCLEON ATVP NUCLEUS	-+	•	+++	0	+	++

Fig. 3.—In dysplasia most of the atypical cells found are hypertrophic deep epithelial cells, some are superficial, a few are intermediate. Very few parabasal dyskaryotic cells are seen while there are no abnormal ("malignant") cells found at all. In carcinoma in situ the relative number of exfoliated atypical cells is changed: very few hypertrophic deep cells, some dyskaryotic superficial, more dyskaryotic intermediate, and many parabasal dyskaryotic cells are seen, while there now are abnormal ("malignant") cells present. In an invasive cancer there are hypertrophic deep cells and fewer dyskaryotic cells in comparison with an increased number of abnormal ("malignant") cells.

In my experience, cells with marked nucleoli seem to be restricted to certain types of invasive carcinomas. All other individual cell types, such as spindle cells, the tadpole cells, and the multinucleated giant cells, for example, have been observed present to a more or less general extent in both invasive and noninvasive lesions.

An examination of the individual cellular criteria shows:

A. The noninvasive carcinoma of the spindle-cell type (Fig. 4) will exhibit relatively the greatest number of dyskaryotic parabasal cells.

B. The noninvasive carcinoma (Fig. 5) of a more mature cell type exfoliates cells which resemble abnormal cells shed from invasive cancers of of spinal or transitional-cell type.

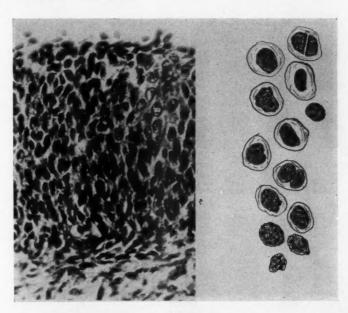


Fig. 4.—Section of a noninvasive carcinoma and the cervical smear showing customarily many dyskaryotic parabasal and abnormal small cells.

C. The borderline cases (Fig. 6), identified as malignancy by one pathologist and dysplasia by another, exfoliate mostly dyskaryotic cells of the superficial and intermediate cell group and only a few or no abnormal and few or no dyskaryotic parabasal cells. To differentiate such cases, we customarily inject estrogens (Figs. 7-10), following a suggestion by Papanicolaou.³⁶

The normal function of the squamous epithelium is the production of glycogen and keratin. In performing this function, the epithelial cells lose the ability to divide. The abnormal squamous epithelium, on the other hand, produces almost no glycogen and keratin, and retains mitotic activity.

Under the influence of estrogens the cytological smears show less inflammatory reaction and no menopausal cell changes. This helps us to distinguish many of the unusual smears which result from a dysplasia from abnormal smears which derive from a cancer. The atypical cells resulting from a dysplasia can, under the influence of estrogens, return to the production of glycogen and keratin and may gradually cease to divide.

It is impossible to say that all metaplasias which do not react to this proliferative test are definitely malignant, as there are conditions, such as pregnancy, wherein this does not hold true. It is, at least, obvious that cervical

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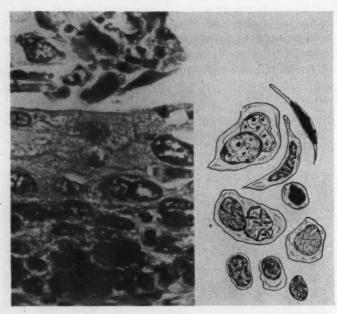


Fig. 5.—Section of a noninvasive carcinoma of a more mature cell type and the corresponding exfoliated abnormal cells. The photomicrograph is taken from a section of the noninvasive carcinoma which involved the cervical glands. The cells on the surface of the section were exfoliated into the lumen of the transformed gland.

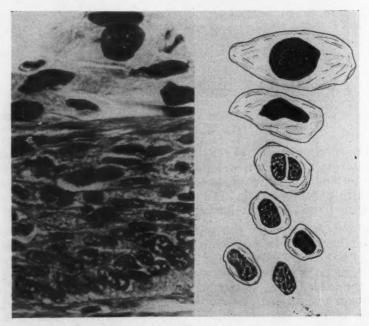


Fig. 6.—Section of a "borderline" epithelium, apparently only a dysplasia, and the corresponding cytological smear. The exfoliated cells are mostly dyskaryotic, still retaining their original form. Lesions which exfoliate only dyskaryotic cells, especially superficial or intermediate dyskaryotic cells, often regress if the cause for the epithelial atypia, e.g., healing erosion, Trichomonas vaginitis, is removed.

corheir terling cancers are never changed by a single injection of estrogens. Furthermore, it is obvious that some difficult borderline cases can be proved benign if the inflammatory reaction is eliminated by administration of estrogens.

In cases with Trichomonas vaginitis (Figs. 11 and 12) we often see a relative increase of superficial and intermediate cell dyskaryosis, but only rarely do we see parabasal cell dyskaryosis. The cellular abnormalities often disappear during or after the therapy.

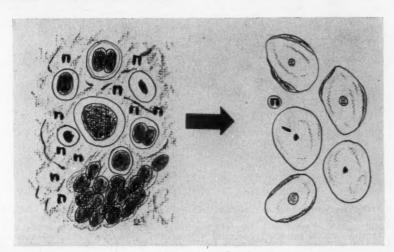


Fig. 7.—Vaginal smears of a patient with an atrophic menopausal smear type before and after a single injection of 10 mg, estradiol benzoate. The smear shows prior to the proliferation test a cytological picture which is often misinterpreted by the less experienced screener: anisocytosis, anisokaryosis, irregular nuclear outlines, disturbed nuclear-cytoplasmic ratio. In addition there are found degenerated leukocytes, abundant coccoid bacteria, and sometimes a few red blood cells. After the proliferation test all these features which make the interpretation difficult disappear and the cells are now easily diagnosed as being normal.

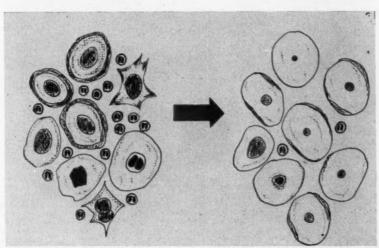


Fig. 8.—Cervical smears of a patient with dysplasia of the cervical epithelium before and after the proliferation test with estrogens. The smears show, prior to the administration of estrogens, many hypertrophic deep cells, some dyskaryotic superficial cells, and many leukocytes. Many of the deep and dyskaryotic cells and most of the leukocytes disappear after the administration of estrogens.

The cytological differentiation which we believe justified according to the potentialities of the technique is divided into four categories (Table II) (not related to the five cytodiagnostic groups of Papanicolaou).

(1) It should be emphasized that the cytological differentiation of invasive from noninvasive cancer is only a suggestive aid. This suggestion is based on the careful evaluation of the surroundings of the epithelial cells, including bacteria, leukocytes, and red blood cells. It is further dependent on a study

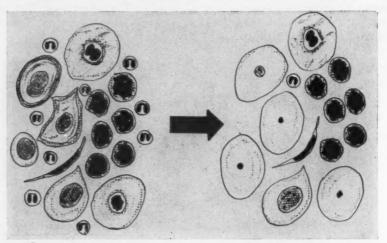


Fig. 9.—Cervical smear of a patient with noninvasive cervical cancer before and after injection of estrogens. The smear prior to the injection shows more leukocytes and more "nonmalignant" epithelial cells of a deeper layer than after the proliferation test with estrogens. Some dyskaryotic and all of the abnormal ("cancer") cells are found to remain after the administration of estrogens. The smears now exhibit the abnormal cells more prominently.

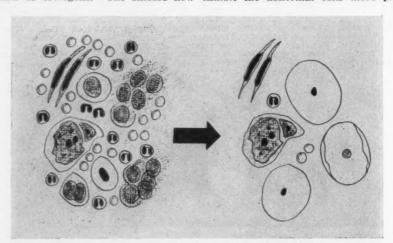


Fig. 10.—Vaginal smears of a menopausal patient with an invasive squamous epithelial cancer of the transitional cell type before and after the proliferation test with estrogens. The smear shows, prior to the administration of estrogens, many degenerated parabasal cells (of the atrophic menopausal type), many leukocytes, and red blood cells. Abnormal cells are not easily detected in the dense grouping of these elements of the smear. After the injection of estrogens this atrophic menopausal smear type is superseded by a more highly proliferated type. There is a marked decrease in the number of leukocytes and red blood cells, whereas the abnormal cells now appear much more prominent than before, although the estrogens have no effect whatsoever on the abnormal cells themselves. The smears appear only more "pure" and the cytological diagnosis can be made with less difficulty or chance for error.

of the relative quantities of normal, dyskaryotic, and abnormal cells and of the site (vagina, cervix, and/or endocervix) from which they derive. Although we have not seen abnormal cells with markedly disturbed nuclear-cytoplasmic ratio, hyperchromatosis and marked nucleoli in noninvasive cancers, we must emphasize that there is no definite criterion in the scope of cytology which could be called "specific" for either an invasive or noninvasive lesion.

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(2) There are few invasive cancers which seem to shed only dyskaryotic epithelial cells. There are on the other hand few noninvasive cancers from which we find an exfoliation identical to that from invasive cancers.

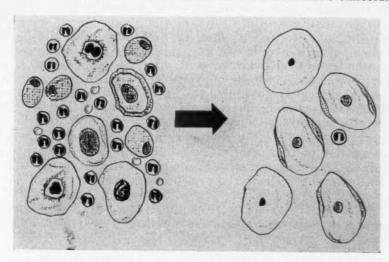


Fig. 11.—Vaginal smear of a patient with Trichomonas vaginitis before and after the treatment of the infection. The drawing at the left shows four dyskaryotic squamous epithelial cells, four protozoa (*Trichomonas vaginalis*, without flagella due to fixation), many leukocytes, and some red blood cells. After the treatment of the Trichomonas vaginitis the dyskaryotic cells disappear.

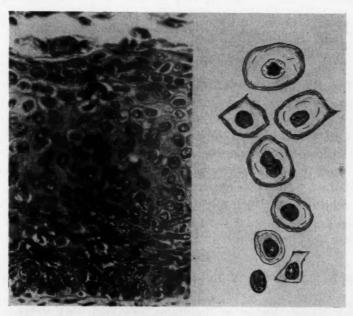


Fig. 12.—Section of an atypical cervical epithelium in the presence of Trichomonas vaginitis and the corresponding cytological smear. Cellular abnormalities due to Trichomonas vaginitis show complete regression after the treatment. If a lesion which was previously diagnosed as a noninvasive carcinoma regresses after therapy for a Trichomonas infection, it is evident that this first diagnosis was wrong, as cancer is an irreversible process.

It seems that some distinct types of invasive squamous epithelial cancers can be more easily identified by the smears as being invasive than can other cell types.

The cytological differentiation seems to be very subjective. Nevertheless, we have, with our suggestive diagnoses, arrived at an accuracy of higher than

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Alclearc canpe of ainva85 per cent, which means that we can accurately determine at least 17 out of 20 invasive cancers as invasive, and at least 17 out of 20 noninvasive cancers as noninvasive.

(3) In borderline cases (dysplasia or noninvasive carcinoma) the injection of estrogens can be helpful in differential diagnoses. If smears prepared after administration of estrogens show fewer or no abnormal cells, or considerably fewer dyskaryotic cells, we are more inclined to call a lesion benign than when the same atypia are present after the application of estrogens. Cancer, even noninvasive cancer, must be considered an irreversible lesion. If injections of estrogens normalize the epithelial structure of a lesion, previously diagnosed as a noninvasive cancer, it is evident that the initial diagnosis was wrong and that we were dealing only with a dysplasia.

4) Dyskaryotic cells often disappear after injection of estrogens, with the discontinuation of the local irritation. Smears with dyskaryotic cells in the presence of Trichomonas vaginalis should be more critically evaluated than smears with dyskaryotic cells in the presence of a healthy vaginal flora. If the epithelial structure of a lesion previously diagnosed as a noninvasive cancer is normalized after the treatment of Trichomonas vaginitis, it is evident that the initial diagnosis was wrong and that we were dealing only with a dysplasia due to local irritation.

TABLE II. CATEGORIES OF CYTOLOGICAL DIFFFERENTIATION

HISTOLOGY	CYTOLOGY			
Dysplasia Noninvasive lesion	Cytology, suggestive of dysplasia. Rule out: noninvasive carcinoma Cytology suggestive of noninvasive carcinoma. Rule out: dysplasia Cytology strongly suggestive of (noninvasive) carcinoma. Rule out: in-			
Invasive cancer	vasive carcinoma Cytology consistent with malignancy (invasive carcinoma)			

Summary

The differentiation of invasive and noninvasive carcinoma of the cervix uteri by means of cytological smears is described and the potentialities of this technique are discussed. The differentiation is based on an evaluation of the surroundings of the epithelial cells, a quantitative relationship of various cell types, and the locality and degree of degeneration of the abnormal cells, but not on any specific cellular criteria. The practical value of this differential analysis is limited. Nevertheless, a diagnostic accuracy of more than 85 per cent can be achieved with such a subjective technique.

Tissue sections were supplied and histological diagnoses were made through the kindness of Dr. Edith L. Potter.

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Discussion

DR. ELIZABETH A. McGREW.-When Dr. James Reagan of Western Reserve University and Dr. Nieburgs, now in Brooklyn, published reports a few years ago indicating that one could cytologically differentiate carcinoma in situ from invasive lesions, I think all of us working in this field were very much interested. Like Dr. Wied, I had sometimes felt that some positive smears had cells which were more wicked than others. After these papers were published, I paid more attention, and now fairly often include these impressions in the description of the slides. My descriptions are not as precisely and systematically coded as Dr. Wied's, but I do sometimes make the statement that cells appear to represent an early noninvasive lesion, or that they almost certainly are derived from an advanced carcinoma.

Dr. Wied is the first really to identify and set down systematically the criteria for making this distinction. Certainly blood and exudate and necrotic debris and the relative numbers of normal and dyskaryotic cells are all factors influencing one's feeling. I had not appreciated any significance in relation to the site of origin of the cells, perhaps because our material is not obtained so precisely from different areas. While I agree that the differences in the cells are in no way specific, I rely more on the degree of abnormality of the cells than Dr. Wied seems to feel is feasible.

There is one point I would like to discuss. Dr. Wied objects to the term "carcinoma in situ." His definitions of carcinoma and carcinoma in situ are descriptions of biological behavior and not histopathologic characteristics. However, pathologists recognize a lesion which many of them are willing to call carcinoma in situ. In this lesion the cells look like carcinoma cells, but they are confined to a position which is superficial to the basement membrane. They can also recognize a similar lesion in which the cells are not quite so carcinoma-like, which some call atypical epithelial hyperplasia or dysplasia or parakeratosis. I think any euphemism can be used as a substitute for carcinoma in situ. However, neither the pathologist nor the clinician knows what this lesion is or what it will invariably do. The advantage to be derived from changing the terminology in no way changes the pathologist's responsibility to report what he sees as concisely and accurately as possible, nor does it change the clinician's responsibility to decide what to do. Any term is dangerous as long as it is not understood.

The estrogen test described by Dr. Wied offers one aid in clarifying some cases in which there are both cytologic and histologic changes which are equivocal. One must clearly define the nature and extent of these lesions before making a decision as to treatment, and much more extensive research is needed before anyone can be certain of the prognosis in any case which shows the histologic features which we now call carcinoma in situ.

DR. JOSEPH T. CHUNG.—Based on his large series of cases, Dr. Wied has proved to us that cytologically there is no difference qualitatively in the cells between preinvasive and invasive carcinoma of the cervix. This concept has long been held by our department at Northwestern. Ayre, however, states that there is a cytologic difference in certain cells between invasive and preinvasive carcinoma. Since histologically the picture between invasive and preinvasive carcinoma is absolutely identical in so far as the individual cells are concerned, then why should the picture in the smear be different? I am happy that Dr. Wied stands on our side of the fence!

On the other hand, Dr. Wied claims that by using other criteria he can differentiate in most cases preinvasive from invasive carcinoma on the smear. The points he stated are nonspecific. For example, he points out that a smear from an invasive carcinoma will never show a healthy vaginal flora. I have seen numerous cases of preinvasive carcinoma associated with Trichomonas vaginitis which did not present a healthy vaginal flora. In such cases, this criterion would not hold true.

Then comes the value of locality of the abnormal cells. This is of only academic interest, because it is an absolute waste of time to take vaginal, cervical, and endocervical smears from a single person, and even more so, to try and estimate the number of abnormal cells in the various smears. Fundamentally the greatest value of vaginal smears is to screen a large group of women for carcinoma and also to detect early carcinoma. Most large clinics do the one-smear technique, so that more patients can be screened. Moreover, according to our experience with over 26,000 patients at Northwestern University, we found that one smear taken from the cervix with an Ayre spatula is sufficiently accurate. Second, we feel that vaginal smears are used only as an aid in detecting carcinoma and that the final diagnosis is a histologic one made on tissue biopsies. From the biopsies, we can readily determine whether the lesion is invasive or preinvasive.

There is one statement made by the essayist that I cannot accept as true. He claims that customarily a cytologist cannot and should not diagnose cells on a smear as malignant

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or benign. According to our experience at Northwestern University, whenever we make a diagnosis of malign mey on the smear, this is practically always confirmed as correct by tissue diagnosis. In our smears with moderately atypical epithelial cells, approximately one out of 5 of these patients turns out to have a malignancy. The lack of more definitive findings in such cases is usually due to the degree of differentiation or to the minimal size of the lesion. In those smears with slightly atypical epithelial cells, about one out of 50 has a malignant lesion. Of course, biopsies are not done in many of the cases from this latter group if a repeat smear is negative. Such smears are frequently found from patients with Trichomonas vaginitis and as soon as the infection is cleared up, the atypia on the smears disappears.

DR. WIED (Closing).—Dr. Chung, there must be some minor misunderstanding. I did not say that the presence of *Trichomonas vaginalis* excludes the existence of a carcinoma. What I said concerning the vaginal flora and cervical carcinoma was that we do not see completely healthy vaginal flora with cytolysis in vaginal smears of patients with invasive cervical carcinoma. I have seen a single patient with a noninvasive carcinoma with healthy flora and cytolysis, but I could never make such an observation in invasive carcinomas.

Dr. Chung said it is a waste of time to make three smears from every patient. It might be a waste of time for cytological laboratories which are not concerned with additional hormonal and bacteriological readings of smears. Let us assume that we might find one subclinical cervical carcinoma in 300 patients in a general population screening. I do not know exactly how much a cytological examination usually costs, but let us assume it might be \$5.00. The cytological detective work for one subclinical carcinoma would then be \$1,500. If we get, however hormonal reading and bacteriological classification from every case, we do not have to count such an amount per cytological detection of a subclinical carcinoma. In my opinion it is a waste of the potentialities of the cytological technique if we should be concerned only with the reading of smears of gynecological material as "positive" or "negative" for cancer. We are at least able in almost every case to tell whether or not the cytological findings are in correspondence with the age of the patient and the menstrual history.

It is necessary to have greater experience to tell androgenic or progestational activity by means of the smears from effects due to slight estrogen deficiency, as an example. But the main cytohormonal types are relatively easily interpreted. Let me illustrate with one example: a patient with secondary amenorrhea. In the office I cannot determine immediately whether the amenorrhea is due to a hypoestrinemia, a relative or absolute hyperestrinemia, or an early pregnancy. If a smear is made and the report is "negative for cancer" then I know only that I have excluded a malignancy, but I still have no information concerning the reason for the secondary amenorrhea. It would be more useful to receive a report in this case which might, for example, read as follows: "Very marked estrogenic effect, no pregnancy cell changes; healthy vaginal flora; no abnormal or atypical cells found." I can now expect that administration of progesterone will produce bleeding.

Invasive cervical carcinomas generally can be most easily detected from cervical smears. The cytological detection of noninvasive carcinomas, however, is usually more accurate in endocervical smears. But the hormonal and microbiological classifications which are in my opinion of extreme value for the gynecologist can be made only from vaginal smears. That is why we make three smears.

There is finally another point where Dr. Chung and I do not agree completely. He calls the cytological reading of smears a diagnosis. I believe Dr. McGrew prefers to call it cytological interpretation, and we call it cytoanalysis. The cytological reading of smears might be accurate in 98 per cent of cases, but it is still not a final diagnosis. As not all exfoliated atypical or abnormal cells necessarily derive from a carcinoma we need to confirm a cytological analysis by another diagnostic procedure, the biopsy. Therefore the cytological reading is not a final diagnosis and the term "cytodiagnosis" is in my opinion overreaching the potentialities of the technique. This last point may, however, be only a problem in terminology. Thank you.

PHASE-CONTRAST MICROSCOPY, AN OFFICE TECHNIQUE FOR PRESCREENING OF CYTOLOGIC VAGINAL SMEARS*†

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THE diagnostic accuracy of exfoliative cytology depends largely on the experience of the cytologist in both his own specialty and the related medical arts. The extent of the clinical application of exfoliative cytology, however, is not dependent on the ability of the cytologist alone. It will depend greatly on the interest of the practicing gynecologist in performing the cytologic smears.

The technique has been known principally since the end of the last century.¹³ Exfoliative cytology gained some publicity in the year 1888, as the medical council of the Kaiser Friedrich III did not believe in the cytologic diagnosis of cancer of the larynx which was made by Dr. von Bergmann. The lesion remained untreated and the Emperor died several months after the first cytologic diagnosis of carcinoma of the larynx. I recently found a monograph on cytodiagnosis on exudates of the year 1908⁹ wherein the author complains about the lack of interest in the excellent procedure of cytologic cancer detection. The modern application of exfoliative cytology, its use in gynecology for cancer detection and hormonal reading, and the special staining procedure introduced by Papanicolaou¹² gave the cytologic technique worldwide publicity.

The diagnostic value of exfoliative cytology is generally recognized. Despite the fact that there has been until now no better technique of early cancer detection in gynecology, the cytologic method is not used to such an extent as it deserves.

The difficulty does not lie so much in the fact that the clinician who is the most important figure in any early cancer detection program is not interested in the procedure, as in the fact that there are not enough cytologic laboratories to handle a general population screening and that the organization of such tremendous facilities would not be economically feasible. Cytologic laboratories are generally operated by a physician who has medical technicians for prescreening of the smears under his supervision. The medical technicians usually review all the slides and pass the atypical and abnormal smears on to the cytologist.

The reports in the literature do not show a completely uniform opinion as to how many women have to be screened per cytologically detected subclinical uterine carcinoma. Assuming that 1 out of 300 screened women will have an

^{*}Supported by the Goldblatt Cancer Research Fund and an Institutional Grant from the American Cancer Society.

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early malignancy, the cost of 299 negative examinations is usually counted per detected carcinoma. This is especially true for these cytologic readings which are concerned only with cancer screening. This is not true, however, for cytologic readings which inform us also about the hormonal situation of the patient and the vaginal flora, because such information helps in diagnosis and treatment in every gynecologic and obstetric case. As great as the importance of early cancer detection might be, it is not the only diagnostic concern of the gynecologist. The diagnosis and treatment of benign diseases and hormonal disturbances represent by far the majority of disorders encountered in gynecologic and obstetric patients. Therefore a diagnostic procedure which is of value for the diagnosis of hormonal disorders and for microbiologic classification deserves more appreciation than a procedure for cancer screening alone. If the cytologic smears are evaluated thoroughly they contribute that much more general information.

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In order to bring to as many women as possible the benefit of one or two cytologic examinations every year we have to reach the following goals:

- 1. The cytologic analysis should give a more general interpretation, such as hormonal reading and microbiologic classification together with the cancer screening, thus offering the clinician more useful and extensive information.
- 2. The cytologic examination of the slides must be relatively inexpensive for the patient and not too time consuming for the clinician.
- 3. The relatively few cytologic laboratories should get for interpretation mainly those cases that represent some uncharacteristic features or abnormalities.

All these three goals can be reached if the first screening of the cytologic smears is put into the hand of the clinician who sees the patient.

It is the purpose of this paper to discuss a technique of exfoliative cytology which can be used by every gynecologist and obstetrician himself as a valuable method of prescreening cytologic material for early cancer detection, hormonal reading, and microbiologic classification. The use of this procedure does not require an extensive training in cytology and does not necessitate the relatively time-consuming processing of the smears.

Cytologic smears are routinely fixed and stained. The fixation is done to preserve the material. Staining procedures are performed either to dye special constituents of the cells, e.g., keratin, fat, glycogen, desoxyribonucleic acid, ribonucleic acid, and enzymes, or merely to make the cells visible for inspection under the normal (bright-field) microscope. A phase contrast attachment in the objectives and condenser of the microscope furnishes a remarkably greater contrast than the bright-field microscope. The increase in contrast is so great that unstained cells are easily visible. The use of non-specific supravital stains as well as nonspecific fluorescent dyes in exfoliative cytology becomes actually worthless for those who examine the specimens with a phase microscope. Supravital staining (e.g., with Giemsa solution) and observation under the normal bright-field microscope might be of some value for rapid cancer screening, but hormonal and microbiologic classifications cannot be made accurately from such material.

Interpretation

The examination of fresh cytologic specimens (Fig. 1) has shown that the unfixed cells exhibit some details of the nucleus and cytoplasm which cannot be seen in fixed and stained material; but experience also has shown that these cytologic features (e.g., mitochondria) have no diagnostic value for the routine cytologic reading of smears.

The office examination is not meant to be a definite cytologic differentiation of cellular anomalies due to carcinoma from atypia due to dysplasias, infections, or unusual menopausal types. The office examination under the phase-contrast microscope should be used only to tell completely normal smears from smears which contain some atypia and therefore require further evaluation.

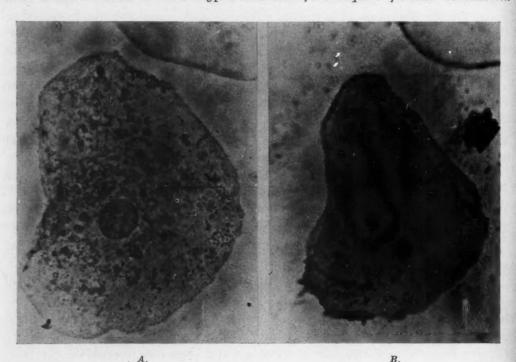


Fig. 1.—Photomicrographs of a superficial noncornified squamous epithelial cell (A) prior to fixation and staining and (B) after fixation and staining. The unfixed cell is considerably larger and exhibits more cellular detail which is, however, insignificant for the routine cytological interpretation. The greatest amount of retraction due to fixation and staining occurs at the periphery of the cell membrane. (Oil immersion of Zeiss phase-contrast microscope and $9\times$ photo-ocular; reduced $\frac{1}{2}$.)

This first screening for typical or atypical cells can be done in a very short time; it can be done in the same length of time we need to look for *Trichomonas vaginalis*, which is a routine part of a gynecologic examination. The detection of *T. vaginalis* (Fig. 2) is much easier under the phase microscope than under the normal bright-field microscope.

Attention is first directed to the determination of the vaginal flora and the evaluation of blood cells.

The smear diagnosis does not give information about the finer classification of bacteria, but the healthy vaginal flora (Bacillus vaginalis Döderlein) can be differentiated from cocci or coccoid bacteria, from fungi, and T. vaginalis. This determination of vaginal flora is not only clinically useful for the treatment of patients with local infections, but also for the cytologic cancer screening. Smears

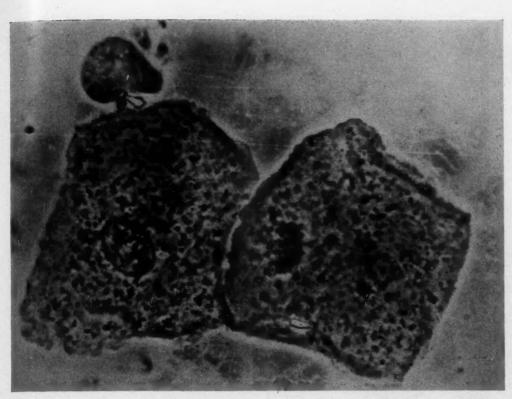


Fig. 2.—Photomicrograph of two superficial noncornified squamous epithelial cells and $Trichomonas\ vaginalis$, prior to fixation and staining.



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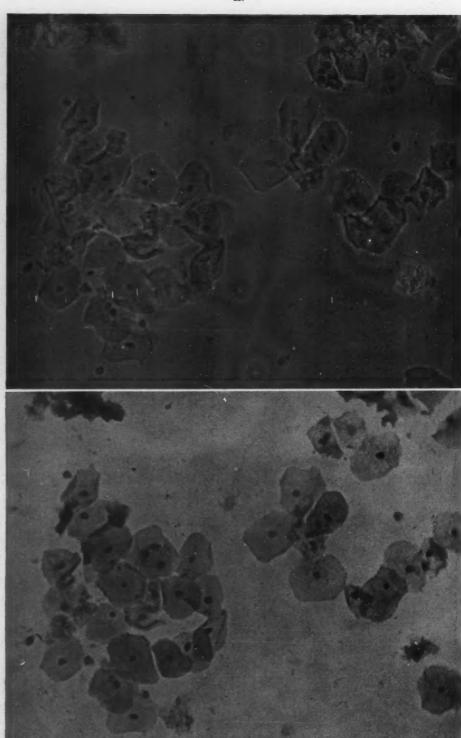
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Fig. 3.—Photomicrograph of an unfixed vaginal smear of a pregnant woman. The cells are markedly folded and crowded. There is an abundance of *Bacillus vaginalis* Döderlein and cellular debris present. No leukocytes are found. The presence of cytolysis which is due to the effect of Döderlein bacilli is always significant for the absence of an invasive cervical carcinoma.



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Fig. 4.—Photomicrographs of vaginal smear (A) prior to and (B) after fixation and staining. The smears were taken at the time of ovulation and show mostly superficial cornified and noncornified cells. The photomicrographs demonstrate that the hormonal evaluation is possible from unfixed as well as from fixed and stained smears. (Zeiss phase-contrast microscope, $20\times$ objective, $9\times$ photo-ocular; reduced %.)

which contain only *B. vaginalis* and show bacterial cytolysis of the epithelial cells are negative for cancer. The bacterial cytolysis is evidenced by a great amount of *B. vaginalis* Döderlein, many free (isokaryotic) nuclei, and usually a complete lack of leukocytes (Fig. 3). A relatively frequent finding is the occurrence of cocci or coccoid bacteria without any inflammatory reaction. This too is usually not seen in smears of patients with invasive cervical carcinomas. The presence of leukocytes and red blood cells is a finding which reclassifies the smear—even in the absence of atypical epithelial cells—from the group "definitely negative for cancer" into the group "most probably negative for cancer."

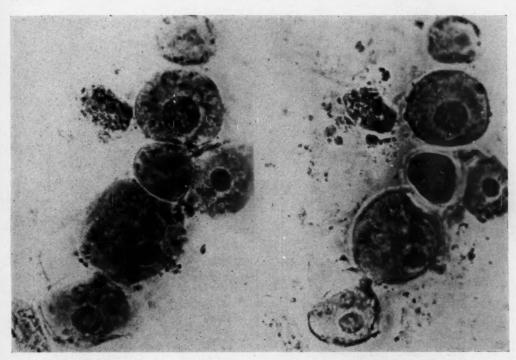


Fig. 5.—Photomicrograph of a vaginal smear of a castrate with atrophic menopausal type. The photograph at the left is taken prior to fixation and the photograph at the right is taken after fixation. Neither smear has been stained. The photomicrographs show 8 squamous epithelial cells of the parabasal cell layers which exhibit usually a moderate anisocytosis and anisonucleosis. (Oil immersion Zeiss phase-contrast microscope, $9\times$ photo-ocular; reduced $\frac{1}{6}$.)

After the evaluation of the vaginal flora and blood cells, attention should be directed to a rough hormonal evaluation of the smears. Accurate hormonal evaluation of the smears generally requires follow-up studies. The classification of the smears in two main groups is however usually possible from every individual vaginal smear: (1) the cytologic findings are in correspondence with the age of the patient and the menstrual history, and (2) the cytologic findings are not in correspondence with the age of the patient and the menstrual history. This rough hormonal reading is made on evaluation of the height of proliferation of the vaginal epithelium. Assuming that estrogenic activity produces a marked proliferation of the vaginal epithelium, smears containing superficial cornified cells (Fig. 4) indicate that the patient is stimulated by estrogens (ovarian or external). The complete lack of estrogenic stimulation is evidenced by the presence of predominantly parabasal cells (Fig. 5) (atrophic menopausal type). The intermediate stages of proliferation, such as the effect of androgens, pregnancy cell types, and slight estrogen de-

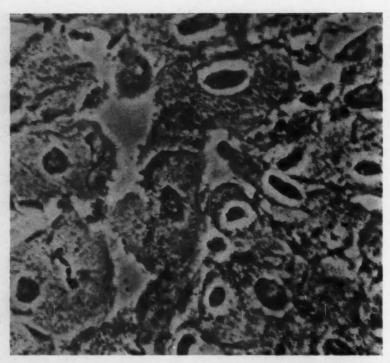


Fig. 6.—Photomicrograph of an unfixed vaginal smear of a patient with noninvasive carcinoma of the cervix. The photograph shows normal squamous epithelial cells of superficial layers and in addition to these normal cells some dyskaryotic superficial cells with nuclei surrounded by a halo. The presense of superficial dyskaryotic cells does not warrant a diagnosis of malignancy, but is always a sign of some epithelial abnormalities. The finding of dyskaryotic cells in fresh specimens definitely warrants a careful cytologic investigation on fixed and stained specimens.

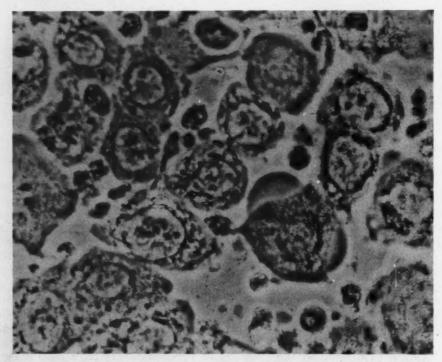


Fig. 7.—Photomicrograph of unfixed abnormal cells in vaginal smear shed into the fornix vaginae from an ovarian carcinoma. The photograph shows poorly differentiated cells with markedly disturbed nuclear-cytoplasmic ratio. Fresh specimens exhibiting cells with disturbed nuclear-cytoplasmic ratio always warrant a careful repetition of smears which should be fixed and stained according to the Papanicolaou technique.

Fig. 8.

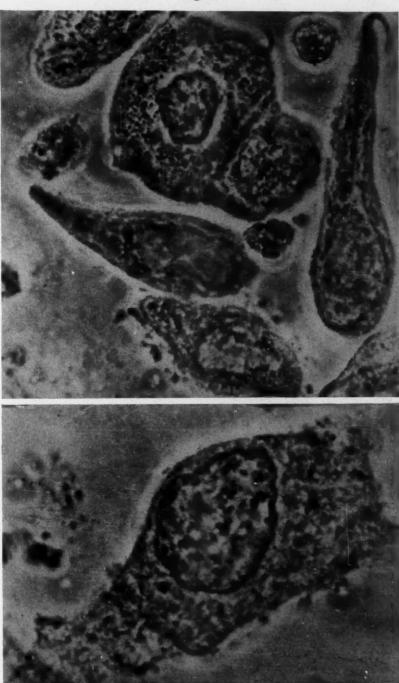


Fig. 9.

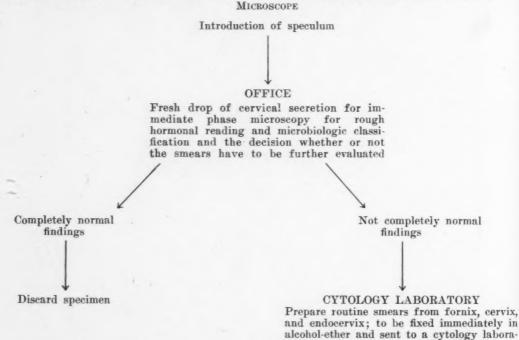
Fig. 8.—Photomicrograph of abnormal cells in vaginal smear of a 20-year-old patient with noninvasive cervical carcinoma. The exfoliated cells show tadpole formation, markedly disturbed nuclear-cytoplasmic ratio, and irregular nuclear outlines.

Fig. 9.—Photomicrograph of an unfixed abnormal cell with irregular nuclear outlines and markedly disturbed nuclear-cytoplasmic ratio. The intrauterine curettage revealed in this case an adenoacanthoma. Irregular nuclear outlines ("mouse-nibbled" nuclear membrane) are almost significant for malignancy.

ficiency, are relatively difficult to evaluate from individual smears. The diagnosis of a marked estrogenic effect, however, or the complete lack of estrogenic stimulation which is possible with the office procedure is often an immediate aid in the diagnosis or treatment of hormonal disorders.

In cytologic screening for cancer, the office examination can be helpful in identifying abnormal cells which may lead to the diagnosis of cancer. In the stained specimens the greatest attention should be paid to the cells with disturbed nuclear-cytoplasmic ratio with hyperchromatic nuclei. In the unstained smears the nuclear hyperchromatosis cannot be detected. Therefore, all cells showing a disturbed nuclear-cytoplasmic ratio (Figs. 6, 7), abnormal nuclear outlines (Figs. 8, 9), and anisokaryosis should be evaluated very carefully. Some nuclear anomalies such as thickening of the nuclear membrane, irregular structure of the nuclear content, and prominent nucleoli are more easily detected in the fresh specimens than in the stained material.

TABLE I. TECHNIQUE OF EXAMINATION OF FRESH SPECIMEN UNDER PHASE-CONTRAST



The technique of examination of the fresh specimen under the phase-contrast microscope in the office or in the laboratory is simple (Table I): Before the routine pelvic examination, the cervix uteri is visualized with a vaginal speculum. With an ordinary wooden tongue blade a drop of fluid from the cervix uteri is removed and put as a drop on a microscopic slide. A small drop of physiologic saline solution or Ringer's solution should be added to the secretion only if needed. A thin cover glass is lightly pressed over the fluid and the material is ready for examination under the phase-contrast microscope. The first screening can be done with the 10x magnification. Higher magnifications are used only for special parts of the smears. It is advisable to use phase attachments which can be adjusted permanently or at least for a reasonable length of time. It is too time consuming to have phase attachments which require readjusting of the condensor after every change of

tory for staining and evaluation

the objectives. The material which is now under the phase microscope is still fresh and can be easily used for cancer screening, hormonal reading, and for the diagnosis of vaginal flora (T. vaginalis), which is a routine part of the gynecologic examination.

As an alternative office technique (Table II), the smears can be fixed immediately in alcohol-ether according to the Papanicolaou technique (one smear from the fornix vaginae, one smear from the cervix uteri, and one smear from the endocervix). The office examination of the fixed but not stained smear can also be made under the phase-contrast microscope. This technique, however, has the disadvantage that some cytologic details are lost due to the fixation. The advantage of this alternative method is, however, that the original Papanicolaou smears would be always available for the classic processing if the necessity should arise.

TABLE II. ALTERNATIVE OFFICE TECHNIQUE Introduction of speculum Prepare routine smears from fornix, cervix, and endocervix; to be fixed immediately in alcohol-ether OFFICE Phase-microscopic examination of the fixed but not stained specimens for rough hormonal reading, microbiologic classification, and the decision whether or not the smears have to be further evaluated Completely normal Not completely normal findings findings OFFICE CYTOLOGY LABORATORY Send to cytology File unstained laboratory specimens

If this procedure is done in a hospital with an attached cytology laboratory the fixed but not stained smears can be used for an immediate cytologic analysis under the phase-contrast microscope in urgent cases. In the laboratory, smears in very urgent cases can be read under the phase microscope and then stained and rechecked as a routine procedure. For the reading of fixed but unstained slides a drop of glycerin or immersion oil is put on the smears, because the dry cells cannot be evaluated properly.

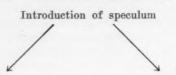
Another alternative procedure (Table III) and also the most careful technique would be to prepare original Papanicolaou smears from every patient regardless of age and menstrual history, and, in addition, to look at a separate

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fresh specimen under the phase-contrast microscope for the immediate interpretation. This last procedure will be restricted however to large institutions.

If for some reason the storage of fresh material should become necessary the slide with the thick drop of fluid should be put into a wet chamber (Petri dish with a wet filter paper). In a wet chamber the fresh material stays undegenerated for several hours.

TABLE III. ANOTHER ALTERNATIVE PROCEDURE



OFFICE

Fresh drop of cervical secretion for immediate diagnostic and therapeutic decisions and decision when the patient has to return

CYTOLOGY LABORATORY

Simultaneously prepare routine smears from fornix, cervix, and endocervix; fix immediately in alcohol-ether and send to cytology laboratory for evaluation

Comment

The recommendation of phase microscopy for the use of the cytologist is not new.¹⁻⁵, ⁷, ¹¹, ²¹ Runge, Voege, and Haselmann¹⁵ and Zinser²⁰ recommended phase microscopy as a substitute for the Papanicolaou technique in the cytology laboratories. Lash and Antonow¹⁰ reported that the phase-optical cytologic interpretation of fresh material was superior in diagnostic accuracy to the Papanicolaou technique in some special cases.

In my opinion the fresh cell examination will not at the present stage of our knowledge be a substitute for the Papanicolaou technique in the cytologic laboratory. In 1951 I made a parallel study on 1,850 specimens which were examined freshly under the phase microscope and then fixed and stained according to Papanicolaou in order to examine the value of both procedures for the cytologic laboratory. This investigation to showed that the fresh cell examination is inferior to the original Papanicolaou technique. But this concerns only the final cytologic analysis of the smears and not the prescreening of the smears in the office of the gynecologist. The gynecologist will generally not be the final interpreter of the cytologic smears just as he is generally not the final interpreter of the histologic material.

The real advantage of the examination of unstained specimens is not that a definite cytologic analysis can be made by a cytologist. The advantage of using the phase-contrast microscope on fresh specimens is in my opinion the fact that the gynecologist can examine immediately to see whether or not the specimens contain enough useful cellular material and to give a preliminary reading in order to eliminate the definitely normal smears. This means, in other words, that the clinician can very well use phase-contrast microscopy for his immediate screening of smears. The gynecologist is accustomed to examining vaginal fluid for *T. vaginalis*. The phase attachment shows also the epithelial cells clearly enough to give a preliminary cytologic evaluation.

The clinician can very well eliminate the completely normal cases, and he can make a microbiologic classification and hormonal reading in almost every case.

By this procedure the clinician has an immediate control and the cytologist will receive only the cases which show abnormalities or which represent some diagnostic problems. Assuming that we can detect one subclinical cancer out of 300 cytologically screened patients I am sure that the office screening can eliminate more than 270 completely normal smears. In other words, such a cooperation between gynecologist and cytologist will permit the clinician himself to discard 90 per cent of all specimens, thus leaving to the cytologist only the not completely normal cases. The cytologist can serve then a ten times greater community with a ten times greater cancer detection rate than before. In large institutions where smears are routinely made from every gynecologic and obstetric patient regardless of age and menstrual history, the phase-contrast examination can be used either in the cytologic laboratory for rapid screening of very urgent cases or in the outpatient department for immediate orientation.

The cytologic examination of fresh secretions under the phase-contrast microscope will not be a substitute for the original technique by Papanicolaou. Phase-contrast microscopy will be only a procedure for immediate screening whereas the final evaluation of the abnormal cases which are detected by the phase-contrast method will have to be done on the fixed and stained specimen.

Summary

A rapid and inexpensive technique with the phase-contrast microscope on unfixed and unstained cytologic smears of secretions of the female genital tract is discussed. This prescreening technique can be used by the clinician without extensive training as an office procedure for bacteriologic classification, hormonal reading, and cancer detection. The phase-microscopic technique enables the gynecologist to eliminate the completely normal cases which will be approximately 90 per cent of all he sees. The remaining 10 per cent must be evaluated by a cytologist. By bringing the cytologic technique into the office of the clinician it can be expected that a considerably greater number of women can be screened than is possible at present and that a relatively higher percentage of subclinical carcinomas will be detected.

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THE ENDOMETRIAL ASPIRATION SMEAR; RESEARCH STATUS AND CLINICAL VALUE*

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WE ARE all aware of the impressive performance of vaginal and cervical smears in the diagnosis of early cancer of the cervix; the high accuracy bids fair to reduce the mortality from this lesion. In the detection of adenocarcinoma of the endometrium, however, vaginal and cervical smears have proved disappointing. Therefore the endometrial aspiration smear has been developed, in an attempt to overcome the intrinsic weaknesses of vaginal smears in endometrial diagnosis.

In 1943, Papanicolaou and Marchetti⁷ described the use of this technique in the diagnosis of cancer and other conditions of the uterus. Herbut and Rakoff,⁸ in 1951, cautioned against the use of endometrial smears as a routine procedure because of the potential dangers in invading the uterine cavity. Kleegman and Speiser⁹ have reported their utilization of the technique in gynecological practice. In order to provide a definitive evaluation of the endometrial aspiration smear as a diagnostic aid in the detection of endometrial cancer, a preliminary study of 125 cases was undertaken at New York University-Bellevue Medical Center in 1952.¹⁰ The results of this work demonstrated the value of the endometrial smear in diagnosing early endometrial carcinoma. They indicated the potential use of the method in the study of other endometrial abnormalities, and it was shown to be a simple, practical office procedure in qualified hands.

Since this work was reported, 4,350 additional cases have been analyzed. Of these, there were 901 in which the cytologic diagnosis was substantiated by tissue examination. On the basis of the analysis of these 901 cases, this paper will attempt: (1) to clarify the cytology of endometrial cells; (2) to prove the value of endometrial smears in diagnosing endometrial cancer; (3) to reaffirm the advantages of the technique over vaginal and cervical smears in evaluating endometrial pathology; (4) to study further endometrial abnormalities other than cancer; (5) to correlate the cytological diagnoses with pathological findings.

The method followed in taking endometrial aspiration smears is clear-cut; the cervix and endocervical canal are painted with an antiseptic solution, and a cannula is introduced into the endometrial cavity. Early in the work, a

^{*}Presented at a meeting of the New York Obstetrical Society, Dec. 14, 1954.

Carey uterine cannula was used. Today a malleable Killian antrum cannula is employed, since it is much thinner, measuring only 2 mm. in thickness, and it passes with greater ease through the internal os (Fig. 1).

The cannula is introduced past the internal os, and, should any difficulty arise, a tenaculum is placed on the anterior lip of the cervix. When the cannula is in the uterus, a 5 or 10 c.c. syringe is attached and gentle suction is applied. The cannula is then removed and the aspirated material is expressed on a clean, dry slide which is immediately immersed in fixative. The smears should not be thick. One or 2 drops on the slide is sufficient, smeared

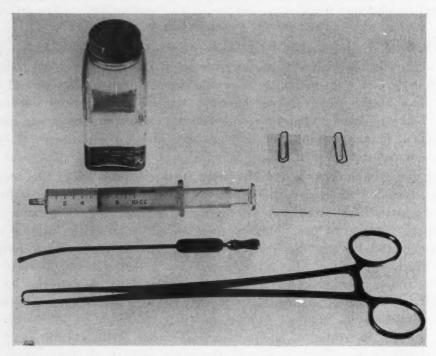


Fig. 1.—Material employed in taking endometrial aspiration smear, including tenaculum, cannula, syringe, bottle of fixative solution, glass slides.

like blood smears with a second glass slide. The staining procedure consists of staining the nucleus with Harris' hematoxylin and counterstaining the cytoplasm with OG6* and EA36† or EA50.

The cytological criteria of malignancy are well known.¹¹⁻¹⁵ Hyper-chromatism, variation in size and shape of the nucleus, and irregularity of the chromatin network are factors in making a positive diagnosis. Diagnoses are reported as "positive," "negative," and "suspicious but negative" in order to provide a rigid classification. If the diagnosis, "suspicious but negative,"

*Orange G — 0.5% solution in 95% alcohol Phosphotungstic acid	100 c.c. 0.015 Gm.
†Light green SF yellowish (water and alcohol soluble) 0.1% solution in 95% alcohol Bismark brown — 0.5% solution in 95% alcohol Eosin yellowish (water and alcohol soluble)	45 c.c. 10 c.c.
0.5% solution in 95% alcohol Phosphotungstic acid Lithium carbonate, saturated aqueous solution	45 c.c. 0.2 Gm. 1 drop

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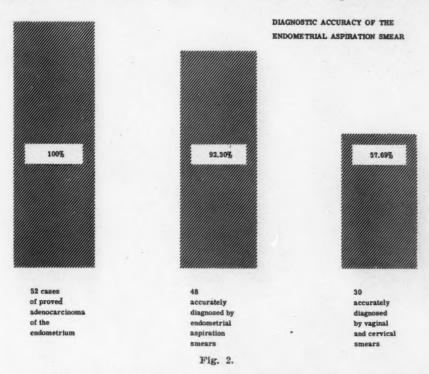
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is made, the doctor is urged to keep the patient under close scrutiny, and to follow with repeat smears at regular intervals. At New York University-Bellevue Medical Center, the diagnosis, "suspicious but negative" is considered an error if the patient later proves to have cancer. The endometrial aspiration smear has shown an accuracy of 92.31 per cent in the present study (Fig. 2).

The cytological picture of adenocarcinoma of the endometrium is as follows: malignant cells are granular, and, on the whole, generally smaller than squamous cells of the cervix. Such cells may be differentiated or undifferentiated depending upon the presence or absence of cellular borders. Differentiated malignant cells conform more closely to those of papillary carcinomas, and undifferentiated cells to those of the more anaplastic tumors.



Differentiated carcinoma cells are characterized by: (1) a distinct cellular border, (2) vacuolated cytoplasm which occasionally pushes the nucleus to one side (these vacuoles often contain small cells, usually leukocytes), (3) larger nuclei, eccentrically rather than centrally located, (4) irregularity of the chromatin network, increase in chromatin content, and variation in size and shape of the nucleus. These nucleochromatin characteristics are evident in all malignant cells (Figs. 3, 4, 5, 6).

Undifferentiated adenocarcinoma cells are defined as follows: (1) they tend to occur in tight groups, (2) cellular borders are indistinct, and vacuolization of the cytoplasm is less marked than in the differentiated cells, (3) the nuclei satisfy the established criteria for malignancy (Figs. 7, 8, 9). On vaginal and cervical smears, the cervical or endometrial origin of undifferential criteria for malignancy (Figs. 7, 8, 9).

Fig. 3.

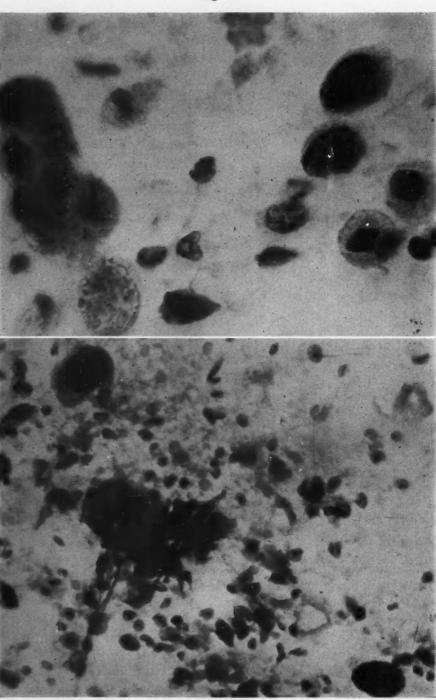


Fig. 4.

Fig. 3.—Differentiated adenocarcinoma showing distinct cell outlines, nuclear hyperchromatism, irregularity of the chromatin network, variation in size, shape, and staining density of the nucleus.

Fig. 4.—Well-differentiated adenocarcinoma showing marked nuclear hyperchromatism and distinct cell outlines.

tiated adenocarcinoma cells is difficult to determine. The endometrial aspiration smear facilitates the diagnosis by fixing the site of the malignancy. This is a most important point.

Fig. 5.

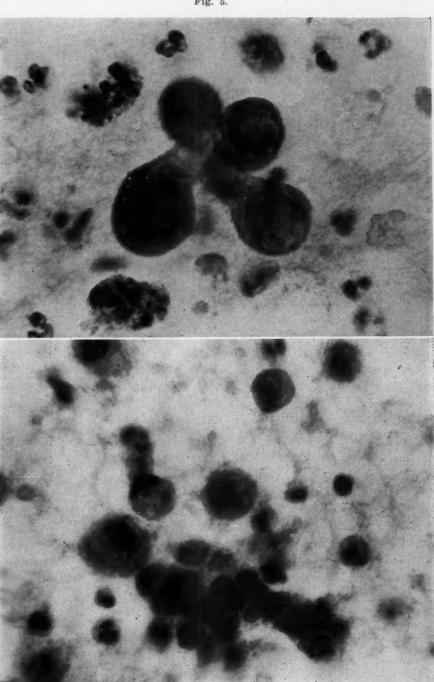


Fig. 6.

Fig. 5.—Endometrial aspiration smear showing a cluster of well-differentiated malignant Fig. 6.—Endometrial aspiration smear showing malignant signet-ring cells.

The nuclei of endometrial carcinoma cells show marked variation in size rather than in shape. Mitotic figures may be seen, a cytological rarity in cervical carcinoma. The tendency to tight clumping of cells is more marked than in cervical cancer.

Am. J. Obst. & Gynec, April, 1956

In the present study, a pattern of malignancy has been observed, particularly of the undifferentiated or anaplastic adenocarcinomas, which is not as definite, cytologically, as is the well-differentiated variety. The characteristics of malignancy are not unmistakable. Cellular outlines are not sharply delineated, and the cytoplasm is not vacuolated. The cells in such carcinomas are smaller, and they do not show the marked variations in size, shape, and staining reaction regularly seen in the usual malignant cells. Only careful study leads the experienced interpreter to conclude that they are malignant.

Generally, in positive endometrial smears, clusters of normal endometrial cells are found in addition to malignant cells. These normal cells, when adenocarcinoma is present, often show evidence of hyperplasia, indicated by extremely large, benign-appearing nuclei and large amounts of cytoplasm (Figs. 10, 11). More than half the positive smears in the 901 cases studied include hyperplastic endometrial cells. It is important, therefore, when endometrial smears are evaluated, that all the endometrial cells present be considered before a diagnosis is made.

To understand the advantages of the endometrial aspiration smear over vaginal and cervical smears in reflecting endometrial changes, the relative accessibility of the cervix and endometrium must be remembered. The accessibility of the cervix to diagnosis is such that the New York City Department of Health has considered having women take their own vaginal smears.* Endometrial cancer is far less accessible to diagnosis but, with the endometrial aspiration smear, the endometrium has been brought, simply, painlessly, and practically into the realm of the accessible.

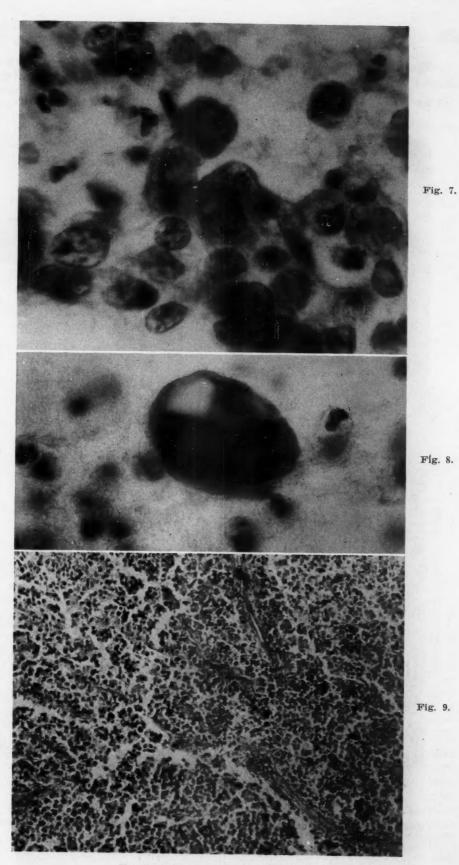
There are other factors responsible for the relative failure of vaginal and cervical smears in endometrial cancer diagnosis. Before they reach the vagina and posterior fornix, desquamated endometrial cells tend to degenerate (Fig. 12). Also, the cervical stenosis which is frequently present in postmenopausal women limits the number of exfoliated cells which pass through the internal os. The cytologist may find the cellular material on vaginal smears insufficient for study. And there is another factor: there is considerable difficulty in differentiating atypical endocervical cells from endometrial cells. The endometrial aspiration smear fixes the source of material on the slide. The

^{*}I have repeatedly cautioned that any premature widespread application of the cytologic method would have disastrous consequences. Before the method can be extended broadly, qualified interpretive personnel must be trained. Lack of such personnel is a problem at the present time. Should the method be universalized before expert interpretive facilities are established, this most important method of early cancer detection may fall into disrepute.

Fig. 7.—Endometrial aspiration smear of undifferentiated adenocarcinoma cells showing the malignant nuclei embedded in a mass of undifferentiated cytoplasm.

Fig. 8.—Endometrial aspiration smear of undifferentiated adenocarcinoma showing vacuolization of the cytoplasm.

Fig. 9.—Histological section of undifferentiated anaplastic adenocarcinoma seen in Fig. 8.



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The following indications have been established for the utilization of the endometrial aspiration smear: metrorrhagia, menorrhagia, menometrorrhagia, and postmenopausal bleeding.

Fig. 10.

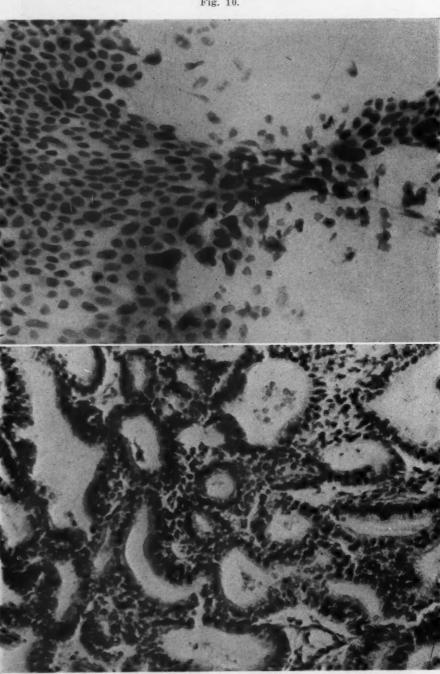


Fig. 11.

Fig. 10.—Endometrial aspiration smear showing hyperplastic cells and the gradual transition to positive evidence of malignancy.

Fig. 11.—Histological tissue section of well-differentiated adenocarcinoma shown in Fig. 8.

The 901 cases in the present report include private and service patients, ranging in age from 26 to 71 years, the average age being 51. Abnormal bleeding was present in every case. One hundred and seventy one, or 18.97 per cent, were bleeding postmenopausally. Of the total studied, 52, or 5.77 per cent, had adenocarcinoma of the endometrium. In the postmenopausal group, 38, or 73.07 per cent, had positive smears.

Of the 52 women who had adenocarcinoma, only 30 cases, or 57.69 per cent, were detected by vaginal and cervical smears. The endometrial aspiration smears accurately detected 48, or 92.31 per cent (Table I). There were 4 false negatives and 5 false positives. These will be discussed shortly.

TABLE I. 901 SMEARS SUBSTANTIATED BY CURETTAGE OR SPECIMEN EXAMINATION

			CE	RVICAL	AND V	AGINAI	SME	ARS		ENDO	METR	IAL SM	EARS	
	TOTAL		ACCURACY		FALSE NEG.		FALSE POS.		ACCURACY		FALSE NEG.		FALSE POS.	
	NO.	%	NO.	%	NO.	1 %	NO.	%	NO.	%	NO.	%	NO.	%
Adenocarci- noma of endo- metrium	52	5.77	30	57.69	22	42.31	4	0.44	48	92.31	4	7.69	5	.55
Endometrial hyper- plasia	146	16.20	53	36.30	93	63.70	9	0.99	110	75.34	36	24.66	12	1.33

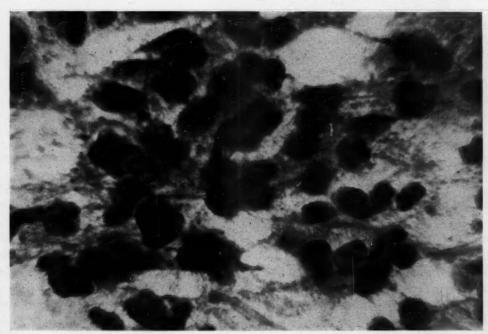


Fig. 12.—Vaginal smear of known adenocarcinoma showing degenerative cells with obscure

In each of the 901 cases studied, curettage or subsequent operation was performed, and the tissue was analyzed. In 698, or 69.17 per cent, curettings were examined. In 203, or 30.83 per cent, both the uterus and curettings were available. Positive smears must always be confirmed by curettage. When endometrial aspiration smears are strongly positive, however, and examination of the curettings is negative, histological examination after operation may still confirm the cytological findings. This diagnostic disparity is usually due to technical difficulties inherent in the operation of curettage.

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When curettings are scanty, the pathologist's diagnosis may be "insufficient material." Material may be lost in the laboratory resulting in an inconclusive report. In contrast, even when uterine material is scanty, the endometrial aspiration produces an even, abundant sampling of exfoliated cells.

There were 6 cases in which adenocarcinoma of the endometrium was repeatedly and consistently diagnosed on the endometrial smears and missed by examination of curettings. In each of these, subsequent removal of the uterus showed adenocarcinoma.

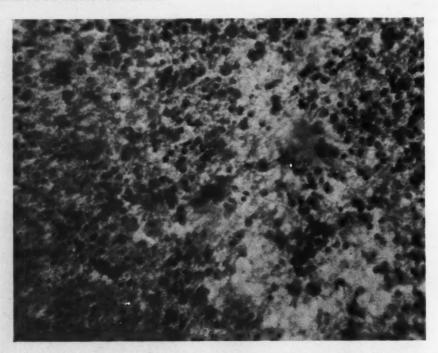


Fig. 13.—Endometrial aspiration smear showing characteristic profusion of exfoliated cells.

In one New York hospital, a routine procedure has been instituted on the gynecological service which may be worth mentioning. In every case of operation for uterine pathology—particularly myomectomy or hysterectomy—vaginal, cervical, and endometrial smears are taken when the patient is admitted. Diagnostic curettage is performed 2 or 3 days before operation. When the specimen is removed, it is reviewed by the departments of gynecology and pathology.

This experience has suggested that diagnostic curettage is often not thorough, and it may explain why an occasional carcinoma is missed. Even the most meticulous operation may fail to explore some of the less accessible endometrial areas—the 2 horns, the top of the fundus, and the anterior wall directly above the internal os. These areas are as productive of exfoliated cells as areas easily accessible to the curette.¹⁷ Moreover, cancer cells, which are less cohesive than normal cells, are more readily exfoliated, and tend to appear in profusion on cytological smears¹⁸ (Fig. 13).

Many general surgeons who do gynecological surgery fail to do preliminary curettage before hysterectomy. Crossen, in performing routine curettage

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before hysterectomy for fibromyomas of the uterus, found in 549 patients 23 who had cancer of the corpus.^{19, 20} It would be helpful if surgeons who do not elect to subject patients to the added expense, anesthesia, and trauma of a preliminary operative procedure, would take routine endometrial aspiration smears before abdominal surgery.

Who is to take endometrial smears? It is felt that they should be taken by specialists. There may be a tendency to aspirate material from the endocervical canal, mistaking it for the uterine cavity. Physicians who are not gynecologically oriented may hesitate to enter the cavity beyond the internal os. In more than 4,350 endometrial smears taken at New York University, not a single instance of perforated uterus, damage, or infection has been encountered. Occasional cramps of short duration have been the only reaction noted.

Thus the endometrial aspiration technique requires that the physician be familiar with the uterine cavity and that he enter it with confidence. In addition, it is important to examine the patient before smears are taken. If the uterus is retroverted or laterally displaced, the malleable cannula must be directed so that no force is necessary for its introduction.

When the procedure is properly carried out, the problem of differentiating between endocervical and endometrial cells is obviated. The cells must be endometrial cells.

All this has direct bearing on and suggests a logical explanation for the 4 false negatives and 5 false positives reported in this study. In one of the false negatives, the endometrial smear was taken from a private patient, and reported as atypical and suspicious for malignancy, but negative. The second false negative was based upon a poorly taken smear, extremely thick, and cytologically obscure. Repeat smears were not obtainable. Two of the false negatives were errors.

Two of the 5 false positives have been ascribed to faulty smear-taking technique, and failure to aspirate material within the uterine cavity. The exfoliated cells seen were probably atypical endocervical cells. Instead of submitting repeat smears in these cases, the doctors elected to perform diagnostic curettage which proved negative in each. The other 3 false positives were errors (Table I).

In 30, or 57.69 per cent, of the 52 cases of adenocarcinoma, hyperplastic cells were also evident. Cytologically, hyperplasia is evidenced by an overabundance of cells. The endometrial cells occur in tight groups, mosaic-like, similar in their morphology to endocervical cells. The cells are three to four times normal size, and their borders are clearly delineated. The nuclei are large, round, and ovoid in shape, often three to four times normal size, but regular and benign in morphology. There is little variation in size and shape. The nuclei stain heavily, but show a smoothly granular chromatin network. Clusters of degenerated endometrial cells are frequent findings. These probably desquamate from the localized areas of necrobiosis present in endometrial hyperplasia. Numerous red blood cells are present. The cell morphology seems to be identical in both endometrial polyps and endometrial hyperplasia (Figs. 14, 15, 16).

For legends see opposite page.

Fig. 14.

Fig. 15.

Fig. 16.

One hundred and forty-six of the 901 patients or 16.20 per cent, had endometrial hyperplasia; 53 of these cases, or 36.30 per cent, were so diagnosed by vaginal and cervical smears. The endometrial smears, on the other hand, were accurate in diagnosing 110, or 75.34 per cent (Table I).

Six cases were reported as atypical hyperplasia, in which the cells show some variation in size and shape. The pathological reports based on curettings in these 6 were "questionable" in each. A second pathologist reported them as "adenoma malignum." A third pathologist reported them as "endometrial Thus the endometrial aspiration smear reflects very early hyperplasia." stages of carcinoma and slight changes in endometrial cell morphology.

Conclusions

A study has been made of the endometrial aspiration smear, in order to determine its accuracy in diagnosing endometrial cancer.

- 1. The results have shown the clinical value of this procedure, which reflects even very early malignant changes.
- 2. In addition, it indicates early hyperplastic changes in the endometrium, and the diagnosis of endometrial hyperplasia made on the basis of endometrial aspiration smears has been validated.
- 3. It is advocated as a routine preliminary procedure in the investigation of abnormal uterine bleeding.

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Fig. 15.—Endometrial aspiration smear showing hyperplastic endometrial cells with large, regular nuclei, two to three times normal size, and large amounts of cytoplasm.

Fig. 16.—Endometrial aspiration smear of hyperplastic endometrial cells.

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Discussion

DR. LOCKE L. MACKENZIE.—Dr. Hecht has shown, as have others, that this method of diagnosis of endometrial cancer is almost as accurate as the diagnosis of cervical cancer by the smear technique. It is not quite as good but only less by 4 or 5 per cent.

The classification that Dr. Hecht has used is extremely rigid. It is much more rigid than Dr. Papanicolaou's classification. As you know, Dr. Papanicolaou classifies the cells as I, II, III, IV, V. Dr. Hecht's classification gives only three types, or perhaps only two, for if he has made the diagnosis of "suspicious" and the patient does have cancer Dr. Hecht considers himself to be in error. This of course may be of more use to the clinician than the five types of Dr. Papanicolaou, but the technique employed is a little more difficult to follow.

I have not always been able to get a cannula into the endometrial cavity. In certain elderly women there is so much stenosis, even with the tenaculum on the cervix, that I have been unable to force the cannula into the endometrial cavity. This does not occur often but I think it should be borne in mind when evaluating the technique.

In addition to this difficulty, I have occasionally been unable to obtain any material after introducing the cannula into the endometrial surface and applying suction.

Dr. Hecht mentioned 6 cases which were diagnosed cytologically as atypical hyperplasia and in these 6 cases, if I understood him correctly, he said the pathological picture showed adenoma malignum. Are these cases included in his false negative diagnoses? If so, then I think the percentage of false negatives may be a little higher than the figure he has mentioned. If, on the other hand, he does not consider the pathological classification of adenoma malignum as being a malignant tumor, of course his statistics remain as he has stated.

DR. EQUINN W. MUNNELL.—Dr. Hecht has presented a very interesting paper on a technique with a very high degree of accuracy. An accuracy of 92 per cent for diagnosing carcinoma of the endometrium is a tremendous improvement over the very poor degree of accuracy by means of vaginal smear alone. This technique of endometrial aspiration should prove of occasional help in discovering that rare case of carcinoma of the endometrium he mentions that has been missed on curettage, although I must say that I would question the technique used by those people who had missed the diagnosis on curettage.

I should like to ask Dr. Hecht if he has compared the relative accuracies of endometrial aspiration and endometrial biopsy in diagnosing carcinoma of the endometrium. If one is going to the trouble of introducing a cannula into the uterus, it is no more difficult to introduce a small endometrial biopsy instrument. I am curious as to whether endometrial aspiration is superior to endometrial biopsy.

Endometrial aspiration, like endometrial biopsy, will be a technique used largely by the gynecological surgeon, since most internists and general practitioners do not have the training and technical ability to utilize this technique.

DR. WILLARD G. FRENCH.—In one of the last cases of adenocarcinoma of the fundus that I operated upon, I had a prior endometrial biopsy which was reported as negative and on curettage proved to be frank carcinoma.

Dr. Hecht spoke of the difficulties of getting beyond the internal os. I know it is a basic question, but I would just like to have him explain how he sweeps the cannula, just what areas he reaches, and the exact technique employed.

DR. WALTER W. BRANDES.—I like Dr. Hecht's idea of approaching the lesion at its site rather than trying to pick it up from cells that have probably degenerated. It seems to me that by doing an aspiration of the cannula you could not aspirate just one area of the cervix, but probably get material from the surface in general.

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DR. HECHT (Closing).—Admittedly it is sometimes rather difficult to enter the endometrial cavity of stenotic, atrophic, postmenopausal cervices, but it does not happen very often.

The objection has been raised that sometimes the material obtained from the endometrial cavity is rather scanty for a proper smear. Usually in the postmenopausal cervix we place the tenaculum on the anterior lip of the cervix, and usually when the cervix is rather stenotic and atrophic we pass a small sound first. We then pass the cannula, which is about the thickness of the smallest sound, or about 2 mm. in diameter. As soon as we go past the internal cervical os we aspirate, pulling back the syringe three or four times. If the uterus is very small, we simply move the cannula around a bit, causing a little bleeding and producing an exfoliation or a casting off of cells from different parts of the endometrial cavity. I believe I mentioned that this procedure is not one intended for the general practitioner. It is an important procedure for the specialist because in many instances we are unable to convince the patient that she may need a curettage, and sometimes it may be medically inadvisable.

Then again, in some patients after the menopause we have found that the material obtained for histologic tissue section has been insufficient and without the aspiration technique repeated curettage would be necessary.

We have not observed any of the traumatic episodes or the pain that have been mentioned. What we have observed have been periodic cramps, which passed very quickly and which were in no way incapacitating. However, at present we do not advocate this procedure as a routine measure. We advocate it only in the presence of abnormalities in bleeding or postmenopausal metrorrhagia.

In the 6 patients in whom the curettage was negative, abnormal bleeding was present, but specimens were removed because of coincidental pathology such as prolapse or fibroids. The carcinomas which were missed by the curettage were found to be coexistent purely on routine section.

NUCLEAR MORPHOLOGY OF CELLS IN HUMAN AMNIOTIC FLUID IN RELATION TO SEX OF INFANT

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(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women)

AS IN mammals generally, it has been well established that the human female has two X chromosomes, the male an X and a Y.¹⁻⁶ The Y chromosome is considerably smaller than the X. Recent studies have shown a structural difference between human female and male somatic nuclei.⁷⁻¹⁵ The difference between these nuclei is believed to depend upon the fusion of heterochromatic portions of the two X chromosomes of female intermitotic cells to form one mass of chromatin, different from what obtains between the X and Y chromosomes in male nuclei.¹³ The mass observed in female somatic nuclei possesses characteristics which set it apart from the more generalized particles of chromatin. It contains nucleic acid mainly of the desoxyribose type.¹⁴

The sex chromatin in the female nuclei is usually planoconvex in outline and is most characteristically seen just within and in contact with the nuclear membrane. At times a small pale area may be noted within the chromatin mass. In some nuclei it appears as a thickened segment of the nuclear membrane. The average size of 100 sex chromatin bodies was found to be 0.7 by 1.2 microns. A mass of comparable size, shape, and position is hardly ever present in human male somatic nuclei.

In man the sex chromatin mass was first observed in the stratum spinosum of skin biopsies from normal females.^{8, 13} Since then most human tissues have been investigated. The characteristic Feulgen-positive, planoconvex, intranuclear body has been reported in 20 to 85 per cent of the cells in females.^{12, 14} Benign tumors and related conditions in females have been found to contain the sex chromatin mass.¹⁶ It has also been observed in neutrophils.¹⁷

Recently, instead of using histological sections, smears of the oral mucosa have been stained successfully to show the presence of the chromatin body in females.^{12, 16} In these reports, the incidence of the atypical chromatin mass in

males ranged from zero to an average of 0.6 per cent.

Clinical applications have dealt with ascertaining the chromosomal basis in anomalies of sex development, and the chromosomal constitution of certain benign tumors.^{13, 18-28} The presence of the definite sex chromatin mass in every female tissue and organ studied, and the accuracy with which the sex can be ascertained cytologically prompted the study of the nuclear morphology of cells in human amniotic fluid in relation to sex of offspring.

^{*}Markle Scholar in Medical Science.

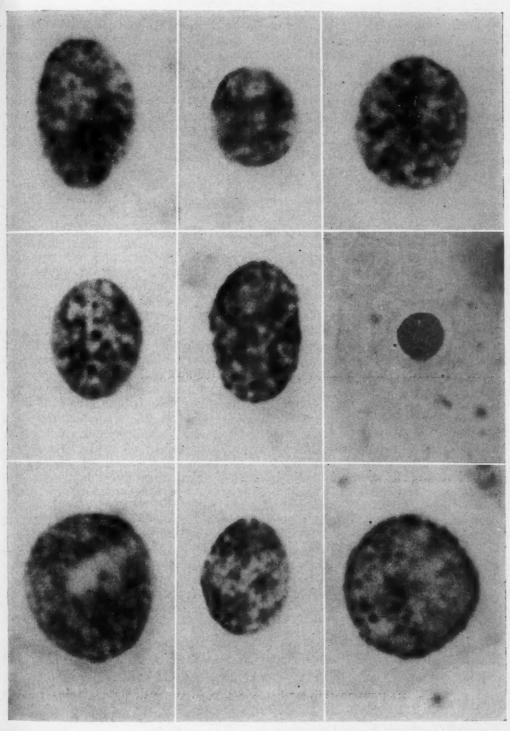


Fig. 1.—Intermitatic nuclei stained with a modified Feulgen technique in smears of cells from amniotic fluids in which male infants developed. (Original magnification ×900.)

Materials and Methods

Ten cubic centimeters of amniotic fluid was obtained with syringe and needle from bulging membranes at the time of low cervical cesarean section, before and after the onset of labor, and from bulging forewaters at vaginal delivery in 40 patients. Twenty of the patients were delivered of normal female and 20 of normal male infants.

The fluid was centrifuged, after which the supernatant portion was discarded. The cells remaining at the bottom of the centrifuge tube were aspirated, placed on a glass slide, and smeared across its surface as thinly and evenly as possible. While still moist, the slides were immersed in modified Davidson's solution²⁵ from ½ to 24 hours. Upon removal from this solution, they were hydrated through absolute, 95, 80, 70, and 50 per cent alcohol, distilled water, and then stained according to a modified Feulgen technique²⁹; a light counterstain was used. Observations were then made under oil immersion.

Results

A number of cells and their nuclei were so deranged and pyknotic that nuclear detail could not be discerned. In every smear, however, there were sufficient nuclei in which the presence or absence of the sex chromatin mass could be determined.

Representative nuclei of cells from the amniotic fluids in which male infants developed are shown in Fig. 1. In none of these smears was the sex chromatin mass seen. Regardless of how the nucleus was rolled a peripheral chromatin mass was not shown. The general distribution of chromatin particles is represented in the various nuclei. The diversity in size, shape, and chromatin particles of the nuclei is in agreement with the possible multiple source of their origin as well as individual variation among cells from a given tissue.

Nuclei of cells from amniotic fluids which contained female infants are illustrated in Fig. 2. In those cells in satisfactory condition for study, 28 to 65 per cent of the nuclei in different samples contained the typical female sex chromatin body. Only those nuclei were counted in which the chromatin mass was seen in profile at the periphery, lying against the inner surface of the nuclear membrane in optical section. Most of these masses were planoconvex in outline; some were very flattened; others were more rounded. The particulate chromatin in the female intermitotic nuclei was usually finer in arrangement and comparatively less conspicuous than in the male nuclei.

Even though the membranes remain intact, after a labor of normal duration in an afebrile patient, the amniotic fluid very often becomes heavily laden with polymorphonuclear leukocytes. These white cells do not prevent, however, the study of nuclear morphology in the other cells.

Comment

The possible sources of origin of the cells in the amniotic fluid include the skin, gastrointestinal, respiratory, genitourinary tracts, umbilical cord, and amnion. Tissues or smears from each of these sources have been found to contain in females the typical sex chromatin mass.^{12, 14, 15} The presence of the mass in intermitotic nuclei of every tissue studied in the female is in accordance with its being formed from union of the two X chromosomes. The degree of variation in morphology of the cells in a given amniotic fluid reflects the varied sites of their origin; however, the cellular chromosomal constitution is

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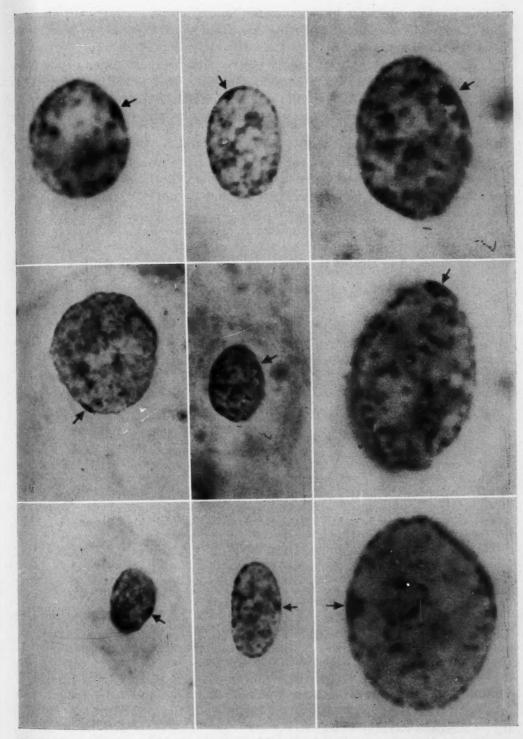


Fig. 2.—Intermitotic nuclei stained with a modified Feulgen technique in smears of cells from amniotic fluids in which female infants developed. Original magnification $\times 900$.)

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identical. Also, the cells in the amniotic fluid from its earliest accumulation should have the same genetic constitution, from which it should be possible to ascertain the chromosomal sex.

With careful study of a properly prepared and stained slide of cells from the amniotic fluid, the sex of the infant should be determined with very little chance of error. Accordingly, the sex of the offspring could be studied in utero in the patient with ruptured fetal membranes and leakage of amniotic fluid.

Summary

Smears were prepared from the cells in amniotic fluid at delivery of 40 patients, 20 of whom had normal female and 20 normal male infants, and stained with a modified Feulgen technique.

Many of the nuclei of the intermitotic cells from all of the fluids in which female infants developed contained the characteristic sex chromatin mass; it was not observed in any of the nuclei of cells from amniotic fluids associated with male offspring.

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PROTEIN-BOUND IODINE AND RADIOACTIVE IODINE (I131) UPTAKE STUDIES IN THE NORMAL MENSTRUAL CYCLE

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IT HAS long been felt by many clinicians¹⁻⁸ that functional alterations of the thyroid gland underlie certain of the menstrual disorders and some obstetric abnormalities. The high incidence of hyperthyroidism and myxedema in women and the effect of these two conditions on the menstrual cycle are well known. Animal experimentation⁹⁻¹² also has yielded a good deal of information, at times contradictory, about the effect of the thyroid on the ovary and vice versa.

With the hope of elucidating some of these problems it was decided to study thyroid function in various phases of the normal menstrual cycle. In the present study the serum protein-bound iodine and I¹³¹ uptake determinations have been utilized as a measure of thyroid function. In general it has been shown¹³ that the I¹³¹ uptake shows a significantly good correlation with the serum PBI concentration in normal subjects and in patients with thyroid disease who have not received therapy.

Material and Methods

Ten apparently normal young women formed the source of this material. Their ages ranged between 27 and 40 years; 8 were multigravidas and nulligravidas. The duration of their menstrual cycles ranged between 25 and 35 days. None of them showed any clinical evidence of thyroid dysfunction. Their dietary habits remained fairly constant during the study. Neither did they receive inorganic iodide in any form other than that present in their usual diet, nor were they given any organic iodine compounds. It has been shown that significant alteration in any one of these factors will affect the levels of the PBI. The following plan of investigation was carried out in each case:

- 1. Complete history and physical examination.
- 2. Complete blood count and urinalysis.
- 3. Serum PBI and I¹³¹ uptake determinations were carried out in the first half of the menstrual cycle, usually on the seventh or eighth day. These were repeated in the second half of the cycle, usually in the premenstrual phase, i.e., within 3 days prior to the onset of the menses.
- 4. Endometrial biopsy was obtained premenstrually to determine the presence or absence of secretory-phase endometrium.
- 5. Each volunteer was required to record her basal body temperature daily on the graph provided.

The serum PBI was determined by the digestion-distillation method of Sobel and Sapsin¹⁶ (modified after Barker's¹⁷ method). Analyses were carried out in duplicate or triplicate until the results agreed within 1 gamma per cent.

I¹³¹ uptake was measured 24 hours after an oral dose of 5 microcuries of I¹³¹. The instrumentation was essentially the same as that described by Bauer.¹⁸

Results (Table I)

All of the individuals studied appear to have had euthyroid levels of PBI falling within the 4 to 8 gamma per cent range, except for No. 7, G. G., who had a level of 8.4 in the proliferative phase of the menstrual cycle. The I¹³¹ uptake fell within the normal range of 10 to 35 per cent. In 7 of the 10 patients, the results of the I¹³¹ uptake and the serum PBI levels showed good correlation. There appeared to be no significant difference between the PBI levels and the I¹³¹ uptake in the various phases of the menstrual cycle.

With the exception of No. 2, J. K., premenstrual endometrial biopsies of all the subjects showed histological evidence of a well-marked secretory phase endometrium. The basal body temperature patterns appeared to show good correlation with the endometrial biopsies.

TABLE I. RESULTS OF STUDY OF PROTEIN-BOUND IODINE AND RADIOACTIVE IODINE UPTAKE IN THE NORMAL MENSTRUAL CYCLE

]	MENSTRU.	AL CYCLI				
			FIRST	HALF	SECON	D HALF		
NO.	NAME	AGE	PARITY	PBI GAMMA %	I131 UPTAKE	PBI GAMMA %	I131 UPTAKE	PREMENSTRUAL ENDOMETRIAL BIOPSY
1	D. H.	33	2	7.0	16.7%	6.6	16.6%	Secretory endometrium
2	J. K.	29	1	7.5	14.7%	4.5	15.3%	Proliferative endometrium
3	D. D.	32	2	6.4	32.0%	6.6	29.3%	Secretory endometrium
4	M. W.	36	2	7.3	27.7%	7.0	22.8%	Secretory endometrium
5	C. E.	33	1	7.0	25.0%	5.5	25.3%	Secretory endometrium
6	A. S.	29	0	5.0	19.0%	7.3	34.5%	Secretory endometrium
7	G. G.	-40	5	8.4	24.0%	6.5	32.0%	Secretory endometrium
8	C. B.	32	4	7.1	24.0%	5.8	32.0%	Secretory endometrium
9	M. M.	27	0	6.3	17.4%	7.3	19.4%	Secretory endometrium
10	A. S.	38	2	6.2	24.2%	6.4	22.7%	Secretory endometrium

Comment

If the level of thyroid activity varies during the proliferative and secretory phases of the menstrual cycle, the variation might primarily involve either the uptake or the discharge of iodine, or both these functions might be altered. Pochin¹⁹ has shown that the iodine taken up by the normal thyroid appears to remain in the gland for many weeks or months before its discharge; hence a phasic monthly variation might not cause appreciable variation in the total iodine content of the gland. He²⁰ has also estimated the I¹³¹ uptake by the thyroid at different phases of the cycle and has not detected any menstrual variation.

There is a paucity of reports in the literature dealing with the PBI in the normal menstrual cycle. Danowski and co-workers²¹ studied 4 women at weekly intervals for periods of one and a half to two months, and reported a trend toward a midcycle rise in PBI with a decrease during the postovulation phase. Heineman and his associates²² found the PBI to be decreased from the

pre- to the postmenstrual phase. They felt that these changes are of too small a magnitude to be statistically significant, especially since a variation of 1 gamma is considered to be a normal deviation in most of the methods used in these analyses.

Our findings are essentially in agreement with those of the aforementioned authors. We feel that, for all practical purposes, fluctuations in the PBI and the I¹³¹ uptake associated with the normal menstrual cycle do not appear to be significant.

The failure of these particular studies to show a cyclic variation of thyroid function in association with the menstrual cycle should not be interpreted to mean that thyroid function could not be related in other ways to the cycle.

Studies concerning thyroid function in the presence of various menstrual disturbances are now under way and will form the subject of a later report.²³

Summary and Conclusions

- 1. Serum PBI and I¹³¹ uptake determinations were carried out in 10 apparently normal young women in the various phases of their menstrual cycles.
- 2. The concentration of the PBI appeared to be relatively constant in both the proliferative and secretory phases of the menstrual cycle. The I¹³¹ uptake by the thyroid gland did not appear to have a phasic menstrual variation. There seemed to be good correlation, however, between the serum PBI levels and the I131 uptake results.

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PLACENTAL BACTEREMIA: A SIGNIFICANT FINDING IN SEPTIC ABORTION ACCOMPANIED BY VASCULAR COLLAPSE*

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ROM June 1, 1940, to May 31, 1954, over 7,000 cases of abortion have been cared for on the gynecological service at Bellevue Hospital. Of these, more than 2,500 have shown clinical evidence of infection of varying severity. Among this group, the outcome has been fatal in 22. An autopsy has been carried out by the Chief Medical Examiner, City of New York, in every instance revealing the well-known fatal extensions of postabortal sepsis: i.e., general peritonitis, parametritis, suppurative thrombophlebitis, septic infarction of the lung, uterine and visceral injury, hemoglobinuric nephrosis due to gas bacillus sepsis, and in one instance an acute chemical nephritis.

Twelve, or more than half of these deaths, occurred in the first five years of this period. Since then we have witnessed a marked decrease in the traditional fatal extensions of postabortal infection from its primary site in the uterus. In the last five years, the mortality has been due in 3 cases to Welch bacillus infection, in 2 (admitted in a terminal state) to uremia, secondary to prolonged anuria in which the Welch bacillus was suspected as a causative agent, and in one to toxic nephritis following ingestion of turpentine.

Since July 1, 1954, there have been admitted to Bellevue Hospital 6 patients, all except one in the second trimester of pregnancy, with ruptured membranes and evidence of infection, whose clinical course has been strikingly identical. With these is included a similar case observed at St. Vincent's Hospital.† Four of them resulted fatally, while 3 patients survived. A pathological finding in some of these patients is most unusual. No description of it has been encountered in recent literature. It is not mentioned in the traditional descriptions of the pathology of postabortal infection by Halban and Koehler, and by Martland. For this reason this material is reported.

For purposes of discussion these cases may be divided into two groups. Group A includes 4 cases in which a rather unusual lesion was discovered, which we have termed placental bacteremia. Group B includes 3 cases in which the clinical picture was similar except in severity and outcome, but in whom this lesion could not be discovered.

^{*}Presented at the Joint Meeting of the Obstetrical Societies of New York, Boston, and Philadelphia in New York City, April 12, 1955.

†This case (No. 4) is included through the courtesy of Dr. Bernard Pisani, Director of the Obstetrical and Gynecological Service, St. Vincent's Hospital of New York City.

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Clinical Picture of Septic Abortion Accompanied by Vascular Collapse

Clinical Background.—The clinical background of these cases is remarkably similar (Table I). In all but one instance, the illness was related in time, and probably in etiology, to a traumatic incident which occurred several days before admission to the hospital. One patient admitted insertion of a rubber catheter into the uterus to induce abortion, and a second told a similar story but retracted her statement when her condition improved. Three stated that they had fallen downstairs, a frequent story of patients with various forms of abortion in this hospital, which is received with the credence it deserves. One patient denied interference, but was known to have demanded termination of pregnancy on two previous clinic visits. Thus the suspicion of interference, though presumptive, is strong.

Following the initial incident, there was the onset of vaginal bleeding of slight degree, often accompanied by leakage of amniotic fluid, and lower abdominal pain. After a variable interval chills and fever occurred, and it was usually the severity of these symptoms which led the patient to seek hospitalization. All but one patient complained of fever of from 8 to 24 hours' duration prior to admission. As Table I shows, the cases fell into no particular age group, and all patients were multiparas. Six of the 7, including all of Group A, were in the second trimester of pregnancy.

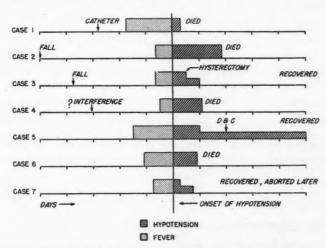


Fig. 1.—Relation of hypotension to fever and initial event leading to abortion. The cases are oriented in time to the onset of hypotension, represented by the central vertical line. In fatal cases the patient dies within 48 hours of the onset of this symptom.

Findings on Admission to the Hospital.—In Fig. 1 the clinical course of these patients is charted in regard to the initial incident, onset of fever, and the appearance of hypotension. The time scales are oriented to the onset of hypotension. It is evident that a fall in blood pressure follows, within 48 hours, the appearance of fever. All but one of these patients were acutely febrile when first seen. Cases 1 and 2 of Group A showed borderline blood pressures on admission, and the subsequent course demonstrated that these patients were on the verge of the hypotensive stage. The remaining patients developed hypotension after admission.

The general physical findings were essentially negative (Table II). No evidence of a cardiac lesion was found, and none of the patients gave a history of heart disease. There was a variable degree of tenderness over the lower abdomen, but the picture fell far short of pelvic peritonitis. On pelvic examina-

tion 5 patients showed evidence of slight bleeding, and in 2 the cervix was slightly dilated. The remaining 2 patients, both in Group A, were admitted before the onset of vaginal bleeding and were found to have a yellowish discharge. The uteri in all cases were enlarged to a size corresponding to the duration of gestation. Two patients exhibited slight adnexal tenderness, while in the remainder no tenderness was found.

TABLE I. CLINICAL BACKGROUND OF PATIENTS WITH SEPTIC ABORTION AND HYPOTENSION

CASE	AGE		DURATION OF PREG- NANCY	COMPLAI	NTS ON AI	INITIAL	RUPTURE OF MEM- BRANES	
NO.	NO. (YEARS) PARITY		(MONTHS)	BLEEDING	PAIN	FEVER		
Group 2	1. Place	ntal Bactere	mia					
1	25	Gravida iv Para ii	4	4 hours	24 hours	24 hours	Catheter, 48 hours	4 hours
2	30	Gravida iv Para iii	4	5 days	8 hours	8 hours	Fall, 5 days	12 hours
3	23	Gravida v Para iii	$4\frac{1}{2}$	None	24 hours	12 hours	Fall, 36 hours	9
4	31	Gravida v Para iv	6	None	None	None	Denied	1 hour
Group 1	B. No P	lacental Baci	teremia.—					
5	44	Gravida ix Para viii	$3\frac{1}{2}$	18 hours	18 hours	24 hours	Fall, 36 hours	18 hours
6	27	Gravida v Para ii	21/2	4 days	4 days	24 hours	Catheter, 4 days	?
7	28	Gravida vi Para v	4	24 hours	24 hours	16 hours	Abdominal trauma	9

TABLE II. ADMISSION FINDINGS IN PATIENTS WITH SEPTIC ABORTION AND HYPOTENSION

		-		GENERAL	PE	LABORATORY				
CASE	TEMP.			PHYSICAL		SIZE OF		FINDINGS		
NO.	(° F.)	PULSE	1	FINDINGS	CERVIX UTERUS		ADNEXA	HGB.	WBC	URIN
Group	A. Plac		acteremi	a. 						
1	103.2	112	88/40	Negative	Purulent discharge Slight bleeding	4 months, tender	Right tender	8.0		Negati
2	104	100	86/60	Negative	Slight bleeding	4 months	Negative	12.0	12.0 No	
3	105.6	140	105/50	Abdomen ten- der	Purulent discharge	4½ months	Slightly tender	11.0		Negatio
4	99.6	96	100/70	Essentially negative	Fluid from cervical os	6 months	Negative	10.8	8,400	Negati
Group	B. No I	Placenta	l Bacter	emia.—						
5	102	104	90/60	Negative	Slight bleeding	3½ months	Negative	12.0	11,600	Negativ
6	102.8	120	118/70	Abdomen ten- der	Moderate bleeding	2½ months	Slightly tender	13.0	11,700	Albumi 1 plu
7	103	138	106/65	Abdomen and costoverte- bral angles tender	Slight bleeding	3 months	Negative	10.0		Clumps WBC

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It seems clear that none of these patients showed, on abdominal or pelvic examination, evidence of significant spread of infection to the neighboring pelvic structures or peritoneum. The essential picture was that of a febrile, threatened or imminent abortion.

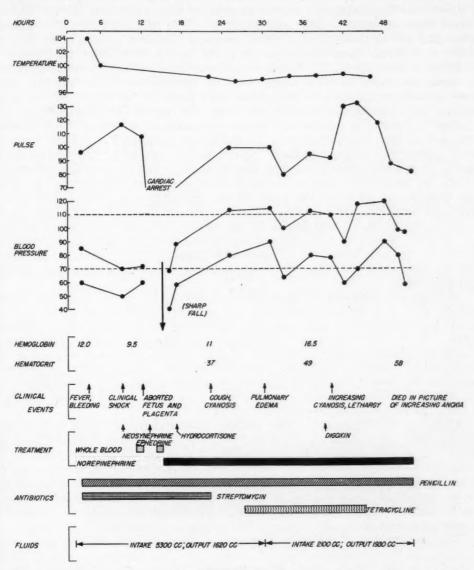


Fig. 2.—Case 2. H. B., septic abortion with A. aerogenes bacteremia. Continuous infusion of norepinephrine was required to maintain blood pressure; sharp fall in blood pressure occurred whenever infusion was discontinued. Note rapid onset of cyanosis and pulmonary edema.

When cases of this kind were first encountered, it was strongly suspected that the patient had unrecorded or concealed blood loss to explain the sudden onset of hypotension. Further experience indicated that this was not the case, for with one exception the blood picture on admission indicated little or no anemia, and these findings remained essentially unchanged in the face of continuing low blood pressure.

Course in the Hospital.—It is clear from the foregoing that the clinical picture of these patients on admission was not unusual, and was not different from that of many cases of septic abortion admitted to our service. Accordingly, they were treated expectantly with bed rest, intravenous fluids, and antibiotics. After a short interval, apparently related to the onset of fever, these patients all developed hypotension. At the beginning they exhibited all the classical clinical signs of shock: cold and clammy skin, rapid thready pulse, anxious facies, and low or unobtainable blood pressure. It soon became clear that this condition differed from shock due to blood loss, in two important respects: (1) blood counts remained normal or indicated increasing hemoconcentration; (2) usual measures to treat shock, such as intravenous fluids, plasma, whole blood, Neo-Synephrine, and ephedrine, had little or no effect on the hypotension. Norepinephrine, used in the form of 8 mg. of the bitartrate per liter of infusion, proved to be the only measure capable of restoring blood pressure to normal levels. The response to this drug was variable, but in some cases the blood pressure could be "titrated" to normal by regulating the rate of the in-When norepinephrine was discontinued, a fall in pressure quickly occurred. In the severe cases of Group A more and more concentrated solutions were required to produce the same effect. Since it was deemed desirable to limit fluid intake in the presence of hypotension and possible renal failure, this led to the use of 16, 32, and finally 48 mg. of the bitartrate per liter of infusion. Two patients in Group A became anuric in the terminal period. Intravenous hydrocortisone and injections of aqueous adrenal extract were tried in several cases because of the impression of overwhelming stress, but had no effect on the clinical picture.

Although it was usually possible to maintain the blood pressure by this artificial means at least temporarily, the general condition of these patients remained grave, and it was apparent that some severe circulatory difficulty existed. In the fatal cases patients became increasingly cyanotic, and signs of pulmonary edema rapidly appeared. Digitalization produced temporary improvement but failed to alter the downward course. This was particularly well illustrated in Case 2, in which pulmonary edema disappeared after digitalization, but the patient remained cyanotic and irresponsive, and seemed finally to die from the progressive effects of anoxia (Fig. 2).

Status of the Pregnancy.—One patient died undelivered, with the placenta still attached. In 4 cases the fetus was aborted shortly after the onset of hypotension, along with portions of the placenta, but in these cases remnants of the placenta remained in the uterus. One patient aborted the fetus shortly after the appearance of hypotension, and at hysterectomy 12 hours later the placenta had not yet separated. One patient in Group B made a gradual clinical recovery

appearance of hypotension, and at hysterectomy 12 hours later the placenta had not yet separated. One patient in Group B made a gradual clinical recovery from sepsis and hypotension, and aborted three weeks later with no evidence of the original syndrome.

Brief summaries of the hospital course of these patients follow.

Case Reports

Group A.—Pathological studies in all of these cases showed the finding of placental bacteremia.

CASE 1.—N. G., a 25-year-old gravida iii, para ii, was admitted on July 16, 1954, complaining of lower abdominal pain, fever, and vaginal bleeding of 4 hours' duration. She admitted the use of a rubber catheter to induce abortion two days before. The last menstrual period was April 25, 1954. On admission, the temperature was 103.2° F., blood pressure 88/40, pulse 112. General physical examination was negative. Pelvic examination showed no vaginal bleeding, but a yellow discharge was noted from the cervix. The uterus was enlarged to the size of a 4 months' gestation, soft and tender. No other masses were

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found, but the right adnexal region was tender. Hemoglobin was 8 Gm. per 100 c.c., red blood count 2.2 million, urine negative. Penicillin and Terramycin were started and the patient sent to the ward.

On this regimen the temperature became normal, but 16 hours later the patient was found to be in clinical shock with no perceptible blood pressure or pulse. Blood counts were repeated and were unchanged. Neo-Synephrine, ephedrine, plasma, and 2 units of whole blood were given without effect on the clinical picture. The patient then aborted a macerated fetus with little blood loss. A norepinephrine infusion was begun, and the blood pressure was brought to 80/30 and the pulse to 120. Despite rapid digitalization, the patient developed signs of pulmonary edema and died 5 hours after the onset of hypotension. There was no urinary output during this interval. Autopsy revealed pulmonary edema, pleural and peritoneal effusions, and a postabortal uterus. No bacteriological studies were done.

CASE 2.—H. B., a 30-year-old widow, gravida iii, para iii, was admitted on Sept. 17, 1954, complaining of vaginal bleeding for 5 days and chills and fever for 8 hours. She attributed her bleeding to a fall while hanging curtains, and denied interference. The last menstrual period was June 4, 1954.

On admission, the temperature was 104° F., blood pressure 86/60, pulse 100. General physical examination was negative. Pelvic examination revealed the cervix to be 1½ fingers dilated, fetal parts palpable. The uterus was enlarged to the size of a 4 months' gestation, and softened. The adnexal areas were negative. The hemoglobin was 12.0 Gm. per 100 c.c., urine negative. Penicillin was started and an infusion begun. Five hours later the patient was found to be in clinical shock, with blood pressure of 70/50, and pulse 116. Neo-Synephrine, followed by plasma and whole blood, was given, but despite these measures the blood pressure continued to fall and 4 hours later could not be recorded. A macerated fetus and placenta were aborted with virtually no blood loss. A cardiac arrhythmia was noted, and for more than 30 seconds there was complete asystole. A norepinephrine infusion was started, and the blood pressure rose to 64/50, with a pulse of 104. Her condition improved slightly, but she remained cyanotic despite nasal oxygen and a blood pressure maintained at 100/80. The blood pressure dropped sharply whenever norepinephrine was discontinued. Intravenous cortisone and aqueous adrenal extract were given without apparent effect. Urinary output remained adequate.

During the next 24 hours the blood pressure stabilized at normal levels with the support of norepinephrine, and urinary output was over 1,000 c.c. Blood counts showed hemoconcentration, with a hematocrit of 58 per cent. Blood cultures revealed Aerobacter aerogenes. A deepening cyanosis was evident, however, and despite digitalization the patient went into pulmonary edema. This cleared to some extent, and the patient died 48 hours after admission apparently of progressive and severe anoxia. Autopsy showed marked edema of all organs, particularly the lungs; pleural and peritoneal effusions; and a postabortal uterus.

CASE 3.—C. C., a 23-year-old gravida v, para iii, was admitted on Oct. 26, 1954, complaining of abdominal pain, chills, and fever. Her last menstrual period was on June 21, 1954. She had been well until the day before admission when her husband threw her downstairs. She denied interference.

On admission, the temperature was 105.6° F., blood pressure 105/50, pulse 140. General physical examination was negative, except for moderate diffuse abdominal tenderness. On pelvic examination there was a yellowish discharge from the cervix, and the uterus was soft and enlarged to the size of a 4½ months' gestation. The adnexal areas were somewhat tender, but not indurated. The hemoglobin was 11 Gm. per 100 c.c., hematocrit 34 per cent, urine negative. An infusion was started, and the patient given penicillin and Terramycin.

Three and a half hours after admission the blood pressure fell to 76/50, with no change in the temperature. The pulse rose to 160. Neo-Synephrine, followed by a transfusion, was given with no change in the blood pressure. Twelve hours later the patient

aborted a 4½ months' fetus, the placenta remaining attached in the uterus. The fetus was macerated and crepitant, and smears showed a gram-positive encapsulated bacillus. Gas gangrene antitoxin was started. A norepinephrine infusion was begun, and the blood pressure could be maintained at 90/50 by this means. The patient was taken to the operating room where attempts to remove the placenta by the vaginal route failed. A rapid supracervical hysterectomy was carried out under cyclopropane anesthesia. Post-operatively norepinephrine was withheld, and the blood pressure remained depressed for 12 hours, after which it returned gradually to normal levels. Her course thereafter was remarkably smooth, with no temperature elevation over 100° F. She was discharged on the twelfth postoperative day, and has remained well.

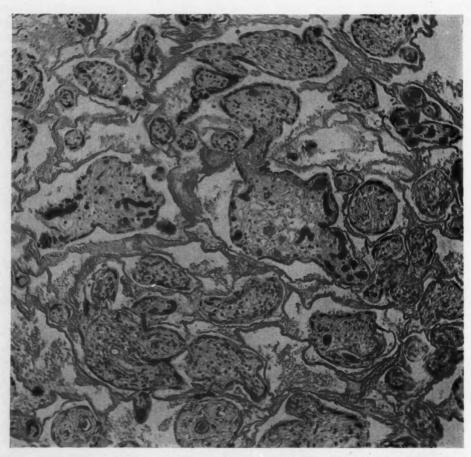


Fig. 3.—Case 4. Placental bacteremia. The dark areas within the villi are fetal vessels, distended with gram-negative bacteria. (Hematoxylin and eosin. ×90; reduced ½.)

CASE 4.—V. L., a 31-year-old gravida v, para iv, was admitted to the St. Vincent's Hospital of the City of New York on Nov. 3, 1954, complaining of leakage of fluid from the vagina. Her last menstrual period was in May, 1954, and she had made several visits to the prenatal clinic, where she demanded termination of pregnancy. On admission, however, she denied interference.

On admission, the temperature was 99.6° F., blood pressure 100/70, pulse 96. General physical examination was negative except for a lipoma of the neck, and a gravid uterus rising to the umbilicus. On pelvic examination fluid could be seen leaking from the vagina, but on speculum examination this could not be clearly ascertained as coming from the cervix. For this reason the vagina was loosely packed and methylene blue placed in the

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bladder. Several hours later the packing was removed, and no trace of dye was seen. It was therefore considered that the fluid was amniotic. The hemoglobin was 10.8 Gm. per 100 c.c. White blood count 8,400, and hematocrit 40 per cent. The patient was placed on the ward at bed rest, and given penicillin.

On the third hospital day there was a sudden elevation of temperature to 106° F., and the patient began to complain of abdominal cramps. General physical examination was again negative, but meconium-stained fluid was noted coming from the vagina. Eight hours after the rise in temperature, she suddenly went into shock, with a blood pressure of 70/50 and only moderate vaginal bleeding. She developed a mottled cyanosis, and numerous petechiae were evident.

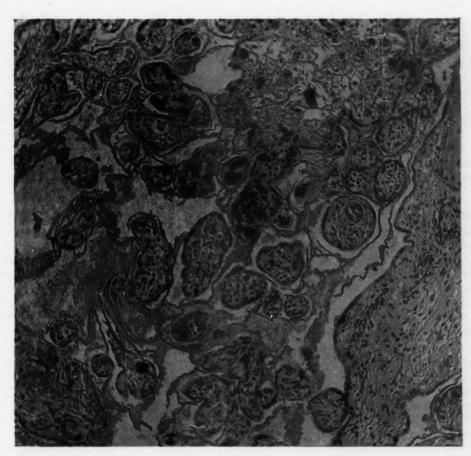


Fig. 4.—Case 4. Placental bacteremia. The fetal vessels are intact and there is no inflammatory reaction in the villous stroma or intervillous space. (Hematoxylin and eosin. ×90; reduced ½.)

A norepinephrine infusion was begun, and with the onset of purpura adrenal cortical extract, vitamin C, and vitamin K were also given. Streptomycin and Aureomycin were started. Despite these measures the blood pressure did not rise above 76/40, and thereafter dropped steadily. She was given three blood transfusions, with a rise in hemoglobin to 13.0 Gm. per 100 c.c. She died, undelivered, 33 hours after the rise in temperature, and 25 hours after the onset of hypotension. Autopsy disclosed marked edema of all organs, particularly of the lungs. There was bilateral hemorrhage in the adrenals. The uterus contained a macerated fetus of 6 months' gestation, with the placenta intact.

Group B.—In these cases the placental tissue showed various degrees of degeneration and infection, but no bacteria were found in the fetal vessels. The clinical course, however, closely resembled that of the cases in Group A, except in severity.

CASE 5.—R. R., a 44-year-old gravida ix, para viii, was admitted on July 18, 1954, complaining of abdominal pain, vaginal bleeding for 18 hours, and fever for 24 hours. Her last menstrual period was April 15, 1954. She fell downstairs 36 hours before admission, and denied interference.

On admission, the temperature was 102° F., blood pressure 90/60, pulse 104. General physical examination was negative. On pelvic examination the cervix was patulous and soft, and the uterus enlarged to the size of a 3½ months' gestation and slightly tender. The adnexal areas were negative. The hemoglobin was 12 Gm. per 100 c.c., and the urine negative. The patient was given penicillin, and placed on the ward at bed rest. Twelve hours later she was found to be in clinical shock, with a rapid pulse and blood pressure of 78/50. Blood counts showed no change since admission, and bleeding was very slight. There was no response to ephedrine, and an infusion containing norepinephrine was started. The blood pressure rose to 110/80, but dropped rapidly each time the infusion was discontinued.

The blood pressure was maintained with norepinephrine during the next 24 hours, and the patient's general condition remained good. Norepinephrine was then discontinued, and the blood pressure stabilized at 85/60. After another 24 hours of observation, dilatation and curettage were carried out. The blood pressure remained depressed for 2 days after operation, but then rose to 108/76. The postoperative course was afebrile, and the patient was discharged on the fourth day after operation.

CASE 6.—L. M., a 27-year-old gravida v, para ii, separated from her husband, was admitted on Sept. 22, 1954, complaining of vaginal bleeding for 3 days and fever for 24 hours. Her last menstrual period was on July 10, 1954. At first she admitted use of a rubber catheter to induce abortion, but later repudiated this statement.

On admission, the temperature was 102.8° F., blood pressure 118/70, pulse 120. General physical examination was negative except for moderate lower abdominal tenderness. On pelvic examination the cervix was soft and closed, and the uterus was soft and enlarged to the size of a 2½ months' gestation. Slight adnexal tenderness was noted. The urine was concentrated and showed a 1 plus albumin. The hemoglobin was 13.0 Gm. per 100 c.c., and the white blood count was 11,760 with a shift to the left.

Terramycin and penicillin were started, and an infusion begun. Three hours later the blood pressure dropped to 90/50, then to 76/50. Blood counts were repeated and showed no change. A norepinephrine infusion was started, with prompt return of the blood pressure to 100/60. Vaginal bleeding was noted, and the patient aborted a 6 cm. fetus and fragments of placental tissue. Norepinephrine was temporarily discontinued, and the blood pressure fell to 40/20. Intravenous cortisone and a transfusion under pressure had no effect. There was a prompt return of blood pressure when norepinephrine was restarted. Streptomycin was begun, and because of a questionable cervical smear for Clostridium welchii, gas gangrene antitoxin was also administered.

Despite these measures, the patient became increasingly cyanotic, developed pulmonary edema, and died 26 hours after admission. At autopsy there was marked edema of the lungs, and congestion of all organs. The postabortal uterus contained fragments of placental tissue.

CASE 7.—J. S., a 28-year-old gravida vi, para v, was admitted on Sept. 30, 1954, complaining of vaginal bleeding for 24 hours, and fever for 16 hours. On the day before admission, one of the patient's children jumped on her abdomen, and this was followed by spotting. Her last menstrual period occurred on June 29, 1954, and she denied interference with the pregnancy.

On admission the temperature was 103° F., blood pressure 106/65, pulse 138. General physical examination was negative, except for slight costovertebral angle tenderness bilaterally.

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On pelvic examination the cervix was soft and closed, and the uterus was soft and enlarged to the size of a 3 months' gestation. The adnexa were negative. The hemoglobin was 10 Gm. per 100 c.c., and the urine showed clumps of white blood cells.

An infusion containing Terramycin was started, and the patient sent to the ward. During the next eight hours she had numerous chills and the temperature reached 105° F. The blood pressure remained normal, and vaginal bleeding was slight. After eight hours the blood pressure suddenly fell to 60/40, and infusion containing norepinephrine was started. The blood pressure rose to 74/50, and the patient was noted to be slightly cyanotic. A repeat blood count showed no change from the findings on admission. Cervical smears showed a few questionable encapsulated gram-positive bacteria, and for this reason gas gangrene antitoxin was given.

Because of the strong impression, gained from previous experience, that the essential difficulty was one of altered hemodynamics due to bacterial toxicity, norepinephrine was discontinued and hemodynamic studies were carried out. During this interval the blood pressure stabilized at 90/50, and thereafter gradually rose without support to 100/70, urinary output remaining normal. All bleeding ceased, and on the fourth hospital day the Aschheim-Zondek test was positive. The patient was discharged on the twenty-second hospital day, but returned 5 days later, when she aborted a macerated fetus and placenta. At this time there was no fever, and the blood pressure remained normal. She was discharged 18 days later, in good condition.

Bacteriological, Pathological, and Autopsy Findings

Bacteriological.—Coliform organisms, Escherichia coli or Aerobacter aerogenes, were found in the blood stream in 4 of the 5 cases in which blood cultures were done. The exception is Case 7 of Group B, the patient who recovered from this syndrome but aborted later, whose original blood cultures showed no growth. In addition, E. coli was found in the placentas in the 3 cases in which this organ was cultured, including Case 7. Table III shows these results.

TABLE III. BACTERIOLOGICAL STUDIES IN PATIENTS WITH SEPTIC ABORTION AND HYPOTENSION

CASE	CE	RVIX	BL	OOD		
NO.	SMEAR	CULTURE	AEROBIC	ANAEROBIC	PLACENTA	FETUS
Group	A. Placental I	Bacteremia.—				
1	-	-		-		-
2	Negative for Cl. welchii	-	A. aerogenes	A. aerogenes	E. coli B. subtilis Enterococci	-
3	Gram-negative and gram- positive bacilli	E. coli Enterococci	E. coli	E. coli	E. coli Enterococci	-
4	-	-	Coli-aerogenes	-	-	-
Group	B. No Placento	al Bacteremia	_			
5	-	-	-	-	-	-
6	Gram-positive bacilli	E. coli Enterococci	E. coli	E. coli	-	Cl. welchi
7	Gram-negative and gram- positive bacilli	E. coli Paracolon bacillus	No growth	No growth	E. coli	

Bacteriological studies carried out on the cervix require further explanation. Smears, stained with Gram stain, were done in 4 cases because Clostridium

welchii infection was suspected. In 3 of these, scattered gram-positive bacilli were noted, some of which showed a questionable capsule. Cl. welchii was not found in the cultural studies of the cervix. In addition to the reports listed in Table III, blood agar plates were smeared with cervical secretion from 6 cases, and read as grossly negative for hemolytic colonies after 24 hours' incubation.

Pathological.—The placentas from severe cases (Group A) showed a lesion which has not been noted as important in our laboratory.* The blood vessels of the villi were distended with gram-negative bacteria which often filled the entire lumen. There was no reaction to these bacteria in the stroma of the villi, and only when these organisms gained access to the intervillous space was an inflammatory reaction seen.

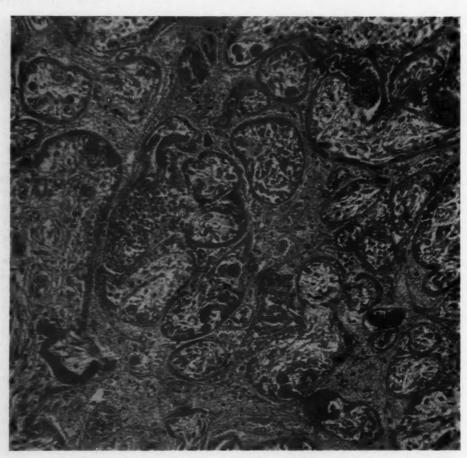


Fig. 5.—Case 2. Placental bacteremia. Bacteria have penetrated beyond the fetal vessel, and there is a localized inflammatory reaction in the stroma of the villus. (Hematoxylin and eosin. $\times 135$; reduced $\frac{1}{2}$.)

Of the cases in which this was found, there were 2 in which the uterus was obtained with the placenta and placental site intact. In these cases the decidua basalis and myometrium showed no inflammatory reaction, and the villi themselves appeared otherwise normal and well preserved. In another case the placenta was passed, but the uterus at autopsy contained fragments at the placental site. Here bacteria were noted only in the vessels of a well-preserved

^{*}A review of cases, occurring in former years, of septic abortion showing hypotension has shown this lesion to be present in several instances.

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villus, while other adherent villi were fibrotic and avascular. In this instance there was also a marked acute inflammatory reaction in the decidua and underlying tissues. The fourth case exhibited a widespread and uniform placental bacteremia with no evidence of inflammatory reaction in the placenta, which was passed spontaneously. The uterus in this case, obtained 24 hours later at autopsy, showed inflammatory reaction in the decidua at the placental site. The circumstances under which some of these tissues were obtained rule out the possibility that placental bacteremia is a postmortem change (Figs. 3-8).

In these cases, therefore, placental bacteremia may exist to a marked degree without inflammatory reaction of the villous stroma or decidua at the placental site. Inflammatory reaction is seen where some of the organisms

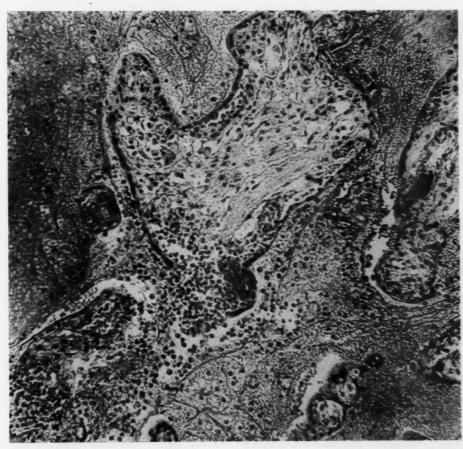


Fig. 6.—Case 3. Placental bacteremia. Bacteria in a fetal vessel near the trophoblastic lining have gained access to the stroma of the villus and to the intervillous space, producing a more extensive inflammatory reaction. (Hematoxylin and eosin. $\times 135$; reduced $\frac{1}{16}$.)

have gained access to the intervillous space, and is uniformly present in the decidua and myometrium in cases in which the placenta has been passed.

Of the remaining cases in which placental bacteremia was not found (Group B), the uterus was available in one and curettings from the placental site in 2 (both of these patients survived). All of these tissues showed an acute inflammatory reaction in the decidua basalis, but the villi showed only slight degeneration or were relatively normal. None of the fetal vessels contained bacteria, and the villous stroma was free of inflammatory cells.

Autopsy.—Autopsies were performed in the 4 fatal cases by the Chief Medical Examiner, City of New York, to whom we are indebted for the opportunity to study this material.

The findings in all of these cases were similar, aside from the adrenals in Case 4, which showed hemorrhage. There was no evidence of heart disease. The lungs were markedly edematous grossly, and on microscopic examination the alveoli contained fluid. The capillary bed showed a marked dilatation and engorgement. Small areas of terminal bronchopneumonia were present in some cases. The livers showed degrees of passive congestion, but were otherwise



Fig. 7.—Case 3. Placental bacteremia. There is an extensive inflammatory reaction in the villous stroma and intervillous space. Many of the bacteria are disintegrating, and staining qualities are lost. (Hematoxylin and eosin. ×135; reduced 1/6.)

essentially normal. The kidneys revealed dilatation and engorgement of the glomerular vessels, and degenerative changes in the tubules, particularly in the proximal convoluted portion. The findings in the uterus have already been described in the discussion of placental pathology, no pathological findings being noted outside the placental site. None of the autopsy material revealed a major focus of infection outside of the uterus.

Unfortunately, none of the fetuses were subjected to autopsy. They were all macerated, and had died in utero.

Management and Treatment

It is apparent from these data that the management and treatment of these cases were not carried out with any single clinical or pathological entity in mind. In the earlier cases internal hemorrhage was suspected as the cause of shock; in other cases the picture suggested collapse due to Cl. welchii septicemia. In each instance the primary consideration was correction of the major apparent clinical difficulty, hypotension. There was no response to ephedrine and Neo-Synephrine. Plasma and blood were ineffective in restoring blood pressure. Norepinephrine was capable of elevating the blood pressure, and in some cases maintaining it at normal levels, but this had little effect on the

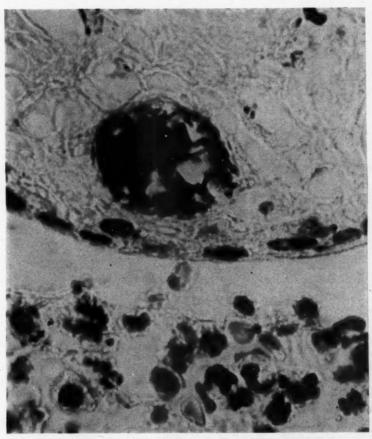


Fig. 8.—Case 1. Fetal vessel containing a large plug of gram-negative bacteria. (Brown stain. $\times 1,350$; reduced $\frac{1}{2}$.)

fatal course of patients in Group A. Indeed, the patients who recovered (Cases 5 and 7) were those who were able to maintain sufficient tension without this drug, after the initial episode.

Hydrocortisone and aqueous adrenal extract, given intravenously, had no appreciable effect. Digitalization was carried out in these cases as a last resort with the appearance of pulmonary edema, and produced no dramatic results. Antibiotics were used in all of these cases, and in some an appropriate drug (Terramycin) was given intravenously on admission. This failed to prevent the

onset of hypotension, or to alter significantly the course once hypotension occurred. Fig. 2 graphically illustrates the course of one of the fatal cases in Group A.

Two patients were treated surgically. One case (Case 5) occurred early in this series; after observation for 48 hours without norepinephrine the blood pressure seemed stabilized at slightly subnormal levels, and curettage was carried out. Hypotension of slight degree persisted postoperatively for 48 hours, but the patient recovered.

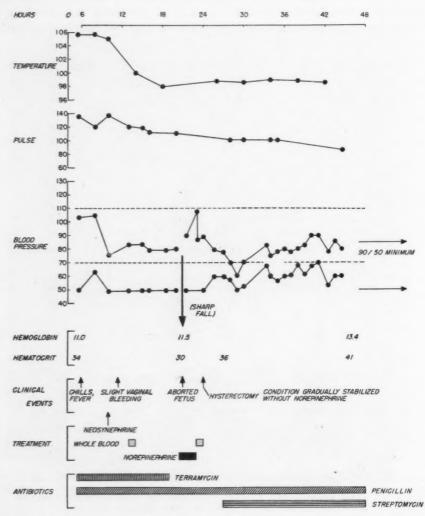


Fig. 9.—Case 3. C. C., septic abortion with $E.\ coli$ bacteremia. Hysterectomy carried out 12 hours after the onset of hypotension. Norepinephrine was not used postoperatively. Note low pulse pressure for first 12 hours after operation.

A second patient (Case 3) was subjected to hysterectomy 12 hours after the onset of hypotension. This was the sixth case encountered, and experience in the previous 5 had impressed us with the high mortality of this condition, and the futility of ordinary conservative management. This operation was carried out as a desperate measure, and in this case was successful, for the patient's condition improved dramatically about 12 hours following operation. Fig. 9 summarizes the course of this patient. For reasons to be discussed later, removal of the uterus is not recommended for all or even the majority of patients with this syndrome, but may be considered.

Comment

This paper is a preliminary report designed to call attention to a clinical syndrome of varying severity seen in cases of septic abortion. While the etiology and pathogenesis are not clear, observation in these cases points to certain probabilities which partially explain the picture.

Against a clinical background of attempted induction of abortion, usually in the second trimester, there appears, after a variable interval, fever. This is followed in 8 to 36 hours by sudden hypotension unrelated to blood loss. The appearance of hypotension in these circumstances is the first clinical finding suggestive of this syndrome. While hypotension seems related to the onset of sepsis clinically, the exact manner in which it is produced is not known. In one case (in which hypotension followed the onset of fever by 8 hours) subsequent clinical and pathological findings suggested the Waterhouse-Friderichsen syndrome, with bilateral adrenal hemorrhage. In the remaining fatal cases, the adrenals were normal.

It seems likely that the hypotension in these cases is related to a bacterial toxin. The organisms cultured from the blood stream and placentas were nearly all of the coli-aerogenes group, and the tissue stains indicated a gramnegative organism in the fetal circulation. Many of the gram-negative bacteria are known to contain a powerful endotoxin, and experimentally this has been shown to produce a profound vasomotor disturbance, terminating in shock.³

One may speculate on the pathogenesis of these cases as follows. At the time of attempted abortion or trauma to the pregnancy, coliform bacteria are introduced into maternal tissues, membranes, and in some cases into the tissues of the fetus itself. It seems significant that the most severe and typical clinical picture is found in cases where a striking placental bacteremia is noted, without significant inflammatory reaction of the decidua or placental tissues. In this respect these cases differ from other instances of infected abortion.

Under these conditions, probably anaerobic, the gram-negative organisms appear to liberate some form of toxin which has profound hemodynamic effects. It is likely that the source of this toxin lies in the fetal circulation, or at least within the uterus, for no other site of infection was found at autopsy in fatal cases. The significance of placental bacteremia probably lies in the fact that it indicates the presence of a large accumulation of bacteria in a location not readily affected by antibiotics, once fetal death has occurred. Fundamentally the placenta represents a membrane estimated to be 7 square meters in area at term,⁴ through which gases and other substances pass back and forth between the fetal and maternal circulation. Under these circumstances it is capable of inundating the maternal blood with the products of bacterial growth and disintegration.

Scattered reports indicate that a similar picture may be found in nonpregnant individuals with septicemias of this kind. Wise and his co-workers⁵ studied 53 cases of septicemia due to gram-negative bacteria, and found a picture of severe vascular collapse in 8.

Whatever the etiology, it is evident that with the onset of hypotension a grave problem in hemodynamics exists. Preliminary studies in 2 patients of this series indicated that significant alterations were: (1) decrease in peripheral resistance, and (2) increase in cardiac output. Moreover, it was clinically apparent that in restoring peripheral resistance by the use of norepinephrine, one did not improve the over-all status. The essential difficulty appears to lie in the pulmonary circulation, as evidenced by the very rapid appearance of cyanosis and pulmonary edema despite supportive measures. It is hoped that hemodynamic studies will be carried out in other cases of this kind, for the finding of increased cardiac output, if confirmed, might distinguish this syndrome from other forms of shock associated with abortion.

From the foregoing, it appears that effective treatment would be directed toward rapid and complete removal of the source of infection and toxicity, by surgical means. However, when the fetus and placenta have been passed, or removed manually or by instruments, and the general condition of the patient remains grave, hysterectomy does not appear rational. When the placenta remains attached and is inaccessible, this procedure may produce dramatic relief as is illustrated in Case 3 of this report.

The course of these patients suggests that surgical intervention, if it is to be effective, should be carried out within 12 hours or less of the onset of hypotension. If delayed beyond this period, it may not influence the course. The latter statement is suggested by the fatal outcome of cases in which the placenta was expelled spontaneously late in the course.*

Summary

A preliminary report is made of seven cases of septic abortion, associated with hypotension not related to blood loss. In severe cases a placental lesion characterized by bacteremia of the fetal vessels was found. Pathological findings, including those at autopsy in four cases, are presented. Management of these cases is discussed.

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^{*}Since the completion of this report a patient, approximately 3 months pregnant with a high fever, who admitted intrauterine manipulation, has been admitted to the Bellevue gynecological service. In anticipation of the syndrome discussed here, the blood pressure was carefully watched, and hypotension developed rapidly. The placenta was immediately evacuated by curettage, and this was followed by a prompt return to a normal clinical picture. Microscopic examination of the tissues revealed placental bacteremia, and cultures of the cervix and blood showed E. coli.

URIC ACID AND ENDOGENOUS CREATININE CLEARANCE STUDIES IN NORMAL PREGNANCY AND TOXEMIAS OF PREGNANCY

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INTEREST in uric acid metabolism developed early in the study of the toxemias of pregnancy. In 1934 Stander and Cadden¹ reported that hyperuricemia was the most characteristic chemical change found in 108 patients
with eclampsia and 40 with pre-eclampsia. They were unable to detect increased urea nitrogen retention, previously reported by Plass,² until the late
stage of eclampsia when renal function was considerably disturbed. These
authors found unusually good correlation between the severity of toxemia
and the blood level of uric acid and concluded that hepatic dysfunction was
present in patients with pre-eclampsia and was responsible for the production of hyperuricemia. Later Cadden and Stander³ studied the urine uric acid
excretion and the blood uric acid levels in 5 women with eclampsia and found
that the 24 hour excretion varied from 0.36 to 0.130 Gm. They stated that
these figures were normal although they made no mention of comparative
studies on normal pregnant women.

Schaffer, Dill, and Cadden⁴ studied renal functions in 12 normal pregnant patients and 10 with pre-eclampsia with simultaneous inulin, Diodrast, urea, and uric acid clearances. In the patients with pre-eclampsia the uric acid clearance was reduced by about one-third and the inulin and urea clearances were lower than those for the normal controls. They noted a similar depression in the other renal clearance studies and stated that the cause of hyperuricemia was the depressed glomerular filtration. Immediately after delivery the blood uric acid fell and the renal clearances rose to normal levels. The authors also cited the earlier work of Nayar, who reported a 13 per cent reduction in the uric acid clearance in eclampsia with a 61 per cent rise in blood uric acid.

Bonsnes and Stander⁵ reported that with few exceptions the 24 hour uric acid and urea clearances were both subnormal during the active phase of preeclampsia and eclampsia but that they returned to normal or nearly normal values by the third to the fourth postpartum day. The average uric acid clearance for 24 hours was 6.4 c.c. per minute before and 10.4 c.c. per minute after delivery. Short-period uric acid and urea clearance determinations also were run and were found to coincide remarkably well with the 24 hour clearance study.

Chesley and Williams⁶ measured the serum clearances of inulin, urea, and uric acid simultaneously in 10 normal pregnant patients near term, and in 10

patients with pre-eclampsia. They noted a reduction of only 25 per cent in the glomerular filtration while the uric acid clearance was reduced 50 per cent, and concluded that the primary cause of hyperuricemia was an increased reabsorption of uric acid in the kidney tubules rather than either decreased destruction in the liver or decreased glomerular filtration.

Chesley objected to the earlier work of Schaffer, Dill, and Cadden because the uric acid clearance was measured in the presence of a plasma Diodrast concentration of the order of 1 to 2 mg. per 100 c.c. of blood. Since Diodrast is an effective uricosuric agent, such a blood level could well give an erroneously high value for uric acid clearance. Moreover, Chesley emphasized that the patients had been on a purine-free diet and that their 24 hour uric acid excretions had been compared to those reported by Burian and Schur in normal patients on uncontrolled diet.

Seitchik⁷ has recently reported renal function studies on 27 normal and 14 pre-eclamptic patients. He found an 18.7 per cent reduction in the glomerular filtration of mannitol and a 47.6 per cent reduction in the uric acid clearance, thus further substantiating Chesley's earlier work.

As early as 1939 Crawford^s studied the plasma uric acid and urea level during labor and the postpartum period in 67 patients. He noted an increase in blood uric acid during labor in both normal and toxemic patients which was proportional to the length and severity of labor. The magnitude of increase was from 0.1 mg. in 3 hours of labor to 4.6 mg. in 73 hours of labor, and the pattern was similar in both the normal and toxemic patients. A fall to normal was noted by the third to the fifth postpartum day. Subsequently Crawford⁹ reported on the uric acid levels in 42 eclamptic and pre-eclamptic patients. A rapid rise in uric acid occurred with convulsions. A similar rise in blood uric acid was noted in patients undergoing shock therapy. He postulated the hyperuricemia was the result of increased muscular exertion and the diminished destruction of uric acid by the liver. Only the patients with moderately increased blood uric acid levels rather than those with the high levels had convulsions.

Dieckmann,¹⁰ in analyzing the problem of hyperuricemia, stressed the importance of factors such as starvation, high-fat diet, blood concentration, oliguria and anuria that may play a part in producing hyperuricemia.

Renal function during normal pregnancy has been studied by many workers but the results and interpretations have not been uniform. Most investigators have found renal function to be within the normal range for nonpregnant women. Ducht, however, states that renal plasma flow as measured by para-aminohippuric acid clearance and glomerular filtration rate as measured by inulin clearance are increased to a maximum during the third to the fourth lunar month. At this time renal plasma flow is approximately 44 per cent greater and the glomerular filtration rate 40 per cent greater than the normal figures for nonpregnant women. Both renal blood flow and glomerular filtration rate decreased to a low level during the last two lunar

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months. Even at this time, however, both are greater than the values in non-pregnancy, especially the glomerular filtration rate which is still 28 per cent greater than that of the nonpregnant state.

The reports of renal function tests with pregnancy toxemias, however, have been even less uniform. Chesley and Chesley¹¹ and other workers^{12, 16-19, 28} have reported mild-to-moderate depression of renal blood flow and glomerular filtration rate with advancing pregnancy toxemia. Corcoran and Page²⁰ were able to find renal depression only in very severe cases of pre-eclampsia. Dieckmann²¹ stated that the urinary excretion of water was decreased in pregnancy toxemia because of renal arteriolar spasm. Dill and associates¹⁷ and Wellen and his collaborators^{18, 19} noted a greater depression of glomerular filtration rate than of renal blood flow. An actual increase in renal blood flow was reported by Kenney, Lawrence, and Miller¹⁴ Bucht and Werko²² found concomitant depression of renal blood flow and glomerular filtration rate with pregnancy toxemia.

In an attempt to determine the value of the creatinine clearance, the uric acid clearance, and blood uric acid levels in the investigation and treatment of pregnancy toxemia the following study was carried out.

Material

Between Sept. 1, 1952, and Aug. 31, 1954, 279 uric acid clearance and blood uric acid determinations were performed in 181 pregnant women almost all of whom were attending the Obstetric Clinic of the Temple University Hospital. A few were private patients admitted to the hospital for the treatment of hypertensive toxemia or uncontrolled weight gain. A single study was obtained on 131 of the patients but on 50 patients from 2 to 7 tests were made during the course of the pregnancy. In 143 of these patients the endogenous creatinine clearance and the uric acid clearance were determined simultaneously 213 times. The entire group of patients was divided into those who were less than 32 weeks pregnant and those who were 32 weeks pregnant or more when the tests were performed. Of the former, the earliest study was made at the tenth week and all but 11 were more than 20 weeks pregnant. Each of the 2 major groups was further subdivided according to the diagnosis at the time of study.

The patients who served as normal controls had been admitted to the hospital because of presumed but not verified premature rupture of the membranes, minimal vaginal bleeding, transverse lie, or similar complications which should not disturb renal function. The patients with pre-eclampsia had been normal prior to the onset of the acute toxemia which was manifested by at least 2 of the 3 cardinal signs: edema, a rising blood pressure, and proteinuria. Nearly all were primigravidas. Essential hypertension was diagnosed in the patients whose blood pressures were elevated during early pregnancy and those with hypertension which was present before they became pregnant. Hypertension with a superimposed toxemia included those with hypertension who developed an acute process characterized by edema, proteinuria, and a further increase in blood pressure during late pregnancy. Sixty-three of the patients in the group of unclassified "toxemia" had gained an unusual amount of weight because of abnormal fluid retention, but none had an accompanying elevation in blood pressure or proteinuria. Five patients had elevations in blood pressure during labor which were not sustained long

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enough to permit their being diagnosed as either pre-eclampsia or hypertension. The urinary protein was normal in each of these but some had gained excessively.

TABLE I. URIC ACID CLEARANCE AND BLOOD URIC ACID

		CID CLEARA			OD URIC AC	
DIAGNOSIS	AVERAGE	RANGE	NO. OF PATIENTS	AVERAGE	RANGE	NO. OF PATIENTS
Pregnancy Less Than 32 Weeks.—						
Normal	18.4 (±4.9)	8.2-27.2	16	$3.2 (\pm 0.8)$	1.8 - 5.2	16
Essential hypertension	14.5 (±5.5)	10.5-31.5	22	$3.7 (\pm 1.2)$	1.8- 6.8	22
Essential hypertension with superimposed acute tox-	, , , ,					
emia	$6.2 (\pm 1.9)$	2.2- 9.0	9	$6.1\ (\pm 1.4)$	4.0- 8.0	9
Pre-eclampsia	4.8 (±1.6)	2.7- 8.8	8	$7.5 (\pm 3.1)$	3.5-12.8	8
Unclassified "toxemia"	$16.7 (\pm 7.5)$	6.9 - 34.3	13	$3.8 (\pm 1.2)$	1.8 - 5.4	13
Pregnancy More Than 32 weeks.—						
Normal	13.0 (±4.0)	6.4-22.3	27	$3.0 (\pm 1.7)$	2.2- 6.8	27
Essential hypertension	14.2 (±6.6)	7.4 - 19.6	26	4.1 (±1.2)	2.0- 8.4	26
Essential hypertension with superimposed acute tox-				(==-/		
emia	$4.5(\pm 2.1)$	1.6- 7.7	8	$5.6 (\pm 1.0)$	4.4- 7.6	8
Pre-eclampsia	$6.5(\pm 2.3)$	3.1-13.7	25	6.0 (±1.4)	3.2- 9.6	25
Unclassified "toxemia"	11.1 (±4.1)	6.2-24.4	47	4.5 (±1.3)	2.3- 9.0	47

TABLE II. ENDOGENOUS CREATININE CLEARANCE

		NCY LESS 2 WEEKS	THAN		NCY MORE 2 WEEKS	THAN
DIAGNOSIS	AVERAGE (C.C./ MINUTE)	RANGE	NO. OF PATIENTS	AVERAGE (C.C./	RANGE	NO. OF PATIENTS
Normal	129 (±41)	77-226	14	108 (±28)	62-155	23
Essential hypertension with	114 (±45)	53-221	21	128 (±46)	67-235	15
superimposed acute toxemia	90 (±37)	48-189	9	60 (±28)	30-121	6
Pre-eclampsia	63 (±20)	40- 91	5	99 (±25)	53-130	21
Unclassified "toxemia"	113 (±33)	74-154	8	110 (±39)	38-211	40

Method

Most of the tests were performed on patients who were hospitalized for the study or treatment of one of the pregnancy toxemias but a few were done on outpatients. The ingestion of fluid and food was not restricted except that breakfast was omitted the morning of the test. Each patient drank 200 c.c. of water every half hour beginning at 6:00 a.m. on the test day to ensure an adequate flow of urine. At about 8:00 a.m. the bladder was emptied through a mushroom catheter which was left in place; the two test urine specimens were collected at the end of the first and second hours. The blood specimen was collected in a clean glass tube during the first half of the test.

The uric acid in the urine and blood was determined by the direct method of Folin and Wu. Creatinine was determined with an Evelyn photometer using alkaline picrate. All laboratory tests were performed by one of two technicians, one working the first year of the study and the other the second year. The maximal renal clearance of uric acid and creatinine were calculated whenever possible. Standard clearances were calculated in a few pa-

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tients whose urinary outputs were so low that the maximal clearance could not be calculated. For proper interpretation the results of the analysis of the two one-hour specimens should coincide within 15 to 20 per cent.

Because there has been so much controversy concerning the need for correcting renal clearance to body surface in pregnancy, we have not corrected our results according to prepregnancy or pregnancy weight. Rather, we have depended upon repeated or serial studies on the same patient to bring out significant changes.

There is some disagreement concerning the accuracy of the endogenous creatinine clearance as a measure of the glomerular filtration rate.^{21, 23-26} It is not adequate for the study of infants, or of adult patients with heart disease or cirrhosis, but the recent studies of Bucht and Werko²² indicate that the endogenous creatinine clearance may be a useful and accurate index of the glomerular filtration rate in the toxemias of pregnancy.

In our laboratory the maximum blood uric acid level for normal pregnant women is 6.0 mg. per cent and the minimum uric acid clearance 10.0 c.c. per minute. The maximum normal blood creatinine is 2.0 mg. per cent. The normal range for endogenous creatinine clearance is from 100 to 140 c.c. per minute during the first 32 weeks of pregnancy and from 90 to 120 c.c. per minute after the thirty-second week of pregnancy.

NORMAL PREGNANCY

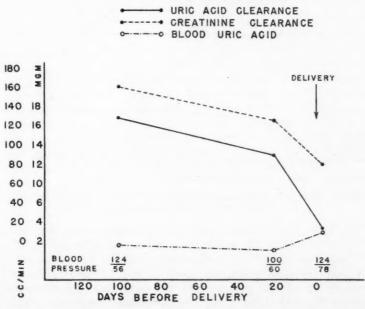


Fig. 1.—Changes in uric acid and endogenous creatinine clearances during the last three months of normal pregnancy.

Results

The results of the uric acid clearance and the blood uric acid levels are shown in Table I. Those for the endogenous creatinine clearance performed simultaneously are shown in Table II.

A. Normal Pregnancy (Fig. 1).—The uric acid clearance in the normal pregnant patients decreased 32 per cent after the thirty-second week of pregnancy from an average of 18.4 to 13.0 c.c. per minute but in both periods it

was above the average figure for nonpregnant women. The levels for blood uric acid remained approximately the same. The endogenous creatinine clearance was altered in a similar manner, falling from 129 to 108 c.c. per minute during the last 8 weeks, a decrease of 16 per cent. The blood creatinine levels were unaltered. These results are similar to the changes in glomerular filtration and renal blood flow as determined by the more precise methods for measuring kidney function and suggest that renal function during normal pregnancy varies in several aspects rather than in a single specific one. It is important that the normal changes be considered whenever one is attempting to interpret the results of renal function studies in abnormal patients. A comparison with the normal figures for a different period of gestation or with those of nonpregnant women is certain to add an additional source of error.

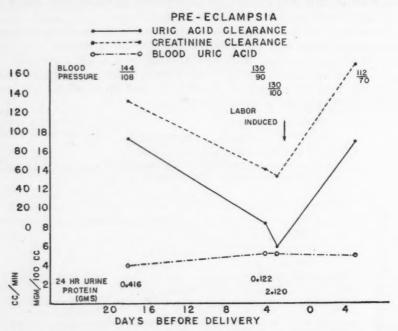


Fig. 2.—Changes in uric acid and endogenous creatinine clearances and in blood uric acid in advancing pre-eclampsia.

B. Pre-eclampsia.—The average uric acid clearance in patients with pre-eclampsia who were less than 32 weeks pregnant was only 4.8 (±1.6) c.c. per minute, 73 per cent less than that for normal women in the same period of gestation. The blood uric acid levels averaged 7.5 mg. per cent. The endogenous creatinine clearance of 63 c.c. per minute was significantly depressed, being 51 per cent lower than that of comparable normal controls. The highest endogenous creatinine clearance was only 91 c.c. per minute as compared to an average of 129 c.c. per minute in the normal patients. The average blood creatinine was 1.5 mg. per cent.

On the surface the difference in the percentage decrease in the two clearances could be accepted as direct evidence of increased reabsorption of uric acid in the proximal tubules during pre-eclampsia but this is not necessarily true. Numerically the glomerular filtration rate, as measured by creatinine clearance, has an eightfold greater value than the uric acid clearance; consequently relative changes may not be manifested so readily. Presumably uric acid is completely filtered through the glomerulus²⁷ and approximately 85 to 90 per cent of the substance is reabsorbed in the proximal tubules.²⁸ It is hard

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to conceive that an organic function operating in the remaining 10 to 15 per cent could be measured as depressed renal clearance with any degree of accuracy, especially if there already exists a depressed glomerular filtration. In serial studies on the same patient the curves representing the changes in the two functions are remarkably similar (Fig. 2). We are reluctant to believe that the reabsorption of uric acid in the proximal tubule is specifically increased in patients with pre-eclampsia.

All but one of the patients studied before the thirty-second week of pregnancy had severe pre-eclampsia. The one exception was a patient with diabetes mellitus with mild toxemia. With the exception of the latter all the pregnancies were terminated before the thirty-second week because of the pre-eclampsia. It was not possible to correlate the severity of the disease with either the depression in renal clearances or the rise in blood uric acid or creatinine.

The average uric acid and creatinine clearances for all the pre-eclamptic patients more than 32 weeks pregnant were higher than those in the group studied earlier in pregnancy. This is quite different from the findings in normal women in whom the clearance rates fall as pregnancy advances. Most of the patients studied during late pregnancy, however, had mild pre-eclampsia, whereas the cases before 32 weeks were, with one exception, severe. When the results in the mild and severe groups are calculated separately it becomes evident that there was greater depression of renal function in those with severe pre-eclampsia regardless of the stage of pregnancy (Table III). The relatively high levels in pre-eclampsia during late pregnancy, therefore, merely reflect the differences in case material between the two groups.

C. Essential Hypertension.—In the patients with uncomplicated essential hypertension the uric acid clearance changed little as pregnancy advanced but the creatinine clearance rose from 114 to 128 c.c. per minute. In the nonpregnant individual with essential hypertension the renal blood flow is reduced because of spasm of the renal arterioles, but the intraglomerular pressure is increased and filtration goes on at a normal or increased rate. The reason for the increased filtration observed in this study is not obvious because renal blood flow was not measured, but it could have been produced by a further rise in arterial blood pressure during late pregnancy.

The blood uric acid was slightly higher than in the normal patients. Hyperuricemia is known to be present in patients with essential hypertension, but the reason is not clear.

D. Essential Hypertension With Superimposed Acute Toxemia.—The most pronounced changes in renal function were observed in the patients in whom an acute process was superimposed upon an existing essential hypertension. The depressions in the uric acid and creatinine clearances were similar to those in patients with pre-eclampsia. In those less than 32 weeks pregnant the uric acid clearance averaged 6.2 c.c. per minute and the creatinine clearance 90 e.c. per minute. The blood uric acid was 6.1 mg. per cent. In those more than 32 weeks pregnant the uric acid was 5.6 mg. per cent. When the patients were subdivided according to the severity of the process (Table IV) the creatinine clearance was more depressed in those with more severe toxemia during both early and late pregnancy. The uric acid clearances showed a similar change in the women more than 32 weeks pregnant, but were slightly higher with severe than with mild toxemia earlier. The groups, as in preeclampsia, are not defined sharply enough to permit evaluation of severity by these tests alone, particulary if a single study is performed. Serial determinations, however, may be more helpful in predicting the development, but not the severity, of a superimposed process (Fig. 3).

TABLE III. URIC ACID AND ENDOGENOUS CREATININE CLEARANCE IN PRE-ECLAMPSIA

	MII	MILD PRE-ECLAMPSIA AFTER 32 WEEKS	PSIA	SEVE	SEVERE PRE-ECLAMPSIA AFTER 32 WEEKS	PSIA	SEVE	SEVERE PRE-ECLAMPSIA BEFORE 32 WEEKS	IPSIA
TESTS	AVERAGE	RANGE	NO. OF PATIENTS	AVERAGE	RANGE	NO. OF PATIENTS	AVERAGE	RANGE	NO. OF PATIENTS
Uric acid clearance									
(c.c./ minute) Blood uric acid	7.2 (±2.5)	3.3-13.7	15	5.4 (±1.6)	2.9-7.5	10	4.5 (±1.6)	2.5- 7.9	1-
(mg. per cent) Creatinine clearance	5.7 (±1.0)	3.2- 6.8	15	6.7 (±1.6)	4.6-9.6	10	7.8 (±3.0)	3.5-12.8	2
(e.e./minute)	99 (±19)	53-157	12	95 (±23)	27-123	6	$61 (\pm 20.6)$	40-91	4

E. Unclassified "Toxemia."—The fall in uric acid clearance from 16.7 c.c. per minute before the thirty-second week to 11.1 c.c. per minute during late pregnancy represents a change of 33 per cent which is similar to that observed in the normal controls. The average creatinine clearance, however, remained constant; 113 c.c. per minute and 110 c.c. per minute. The reason for this variation could not be determined by the tests performed in this study. The patients included under the diagnosis of unclassified "toxemia" probably represent a less homogenous group than do the others. Most of these women were studied because of an abnormal fluid retention, but others had only unstable blood pressures. Even when the latter are eliminated from the calculation, however, the results of the renal function studies remain unchanged.

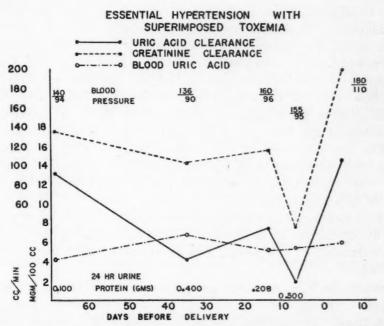


Fig. 3.—Changes in uric acid and endogenous creatinine clearances and in blood uric acid in essential hypertension with superimposed acute toxemia.

TABLE IV. URIC ACID AND ENDOGENOUS CREATININE CLEARANCE IN ESSENTIAL HYPERTENSION WITH SUPERIMPOSED ACUTE TOXEMIA

	M	ILD TOXEMI	A	SE	VERE TOXE	MIA
TESTS	AVERAGE	RANGE	NO. OF PATIENTS	AVERAGE	RANGE	NO. OF PATIENTS
Before 32 Weeks.—				~		
Uric acid clearance						
(c.c./minute)	$5.7 (\pm 2.2)$	2.2-9.0	5	6.3 (±1.7)	4.4-8.3	4
Creatinine clearance	, ,					
(c.c./minute)	99.0 (±41)	48-181	3	73 (±20)	52-94	3
Blood uric acid	` ′			,		
(mg. per cent)	$5.8 (\pm 1.3)$	4.0-7.3	5	$6.6 (\pm 1.3)$	4.4-8.0	4
After 32 Weeks	``					
Uric acid clearance						
(c.c./minute)	$5.7(\pm 2.2)$	1.8 - 7.5	5	$3.5(\pm 1.3)$	1.6-6.0	3
Creatinine clearance						
(c.c./minute)	$74 \ (\pm 5.6)$	35-121	3	$51 (\pm 16.5)$	30-81	3
Blood uric acid						
(mg. per cent)	$5.0 (\pm 0.3)$	4.4-5.4	5	6.1 (±1.1)	4.6-7.6	3

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Comments

The results of this study on uric acid and creatinine clearance during normal pregnancy indicate that the renal excretion of these substances parallels the kidney function as measured by the determination of glomerular filtration and blood flow by more precise methods. The excretions of both creatinine and uric acid reach a maximum before the thirty-second week of pregnancy and then decrease during the last few weeks before delivery. These normal variations must be considered where one is attempting to evaluate the results of the tests in abnormal patients. The blood levels of uric acid and creatinine should not be elevated during normal pregnancy.

There is considerable change in renal function in patients with preeclampsia-eclampsia. The most obvious causes are alterations in renal hemodynamics due to vascular spasm and, in advanced stages of the condition, to hemoconcentration. The glomerular filtration is certainly decreased as evideneed by the low clearances of creatinine observed in this study and of different substances in others. This could occur if renal blood flow were reduced either by vasospasm or by hemoconcentration, if the filtration fraction were reduced regardless of the cause, or if the capillary basement membrane were thickened. The low clearance of uric acid in patients with pre-eclampsiaeclampsia has been attributed to an increased tubular reabsorption of the material rather than primarily to a change in the amount filtered through the glomerulus. In this study, however, the observed changes in the creatinine and the uric acid clearances in pre-eclamptic patients parallel each other, suggesting that an alteration in glomerular filtration is a significant factor in reducing the excretion of uric acid. This is in accord with the findings of Bucht and Werko.22

The depression in both the clearances tends to be greater as the severity of pre-eclampsia increases but the range is too wide to permit classification by these tests alone. The highest uric acid clearance in a patient classified clinically as having severe pre-eclampsia was 7.5 c.c. per minute and the lowest in mild pre-eclampsia was 3.3 c.c. per minute.

Blood uric acid levels are less reliable than the clearance studies in attempting to evaluate severity even though they tend to be higher in severe than in mild pre-eclampsia. The clinical findings often were similar in those with blood levels of 8.0 to 9.0 mg. per cent and those with only 6.0 to 7.0 mg. per cent. In some of the patients with the most severe toxemias the level was as low as 6.0 mg. per cent. Hyperuricemia in pre-eclamptic patients was invariably associated with depressed clearance but the reverse was not necessarily true. In some patients with pre-eclampsia, even in advanced stages, the uric acid clearance was considerably reduced even though the blood level was within the normal range. It is obvious from these results that the blood uric acid level alone gives little information concerning the ability of the kidney to excrete the material.

In the pre-eclamptic patients upon whom repeated studies were run, both the uric acid and the creatinine clearances remained low until the pregnancy

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terminated even though clinical improvement was observed. A sudden decrease in these clearances was of some value in predicting the subsequent development of pre-eclampsia in normal women and in those with fluid retention. Depression was occasionally observed 2 or 3 weeks before the clinical signs could be detected but this was not always the case.

In uncomplicated essential hypertension the elevated glomerular filtration of early pregnancy was maintained during the last few weeks before delivery, indicating that the mechanism is quite different from the normal. This is similar to the glomerular function in nonpregnant individuals with hypertension in whom filtration is normal or increased despite a reduction in renal blood flow because the maximum spasm probably occurs in the efferent glomerular arterioles which of course increases the intraglomerular pressure and thereby enhances filtration. The fact that the uric acid clearance remained virtually unchanged also suggests that alterations in this function are to a great degree dependent upon changes in glomerular activity. When acute toxemia was superimposed upon chronic hypertension the changes in renal function were similar to those observed in patients with pre-eclampsia but in general tended to be more pronounced. This suggests that the two acute processes are of a similar nature. It is impossible, however, with the clearance tests alone to differentiate one from the other.

The studies in patients with unclassified "toxemia" provided little information which was helpful either in diagnosis or in prognosticating the final outcome. This is not surprising since most individuals who fall into this classification are those whose pregnancies are probably fundamentally normal but who demonstrate changes such as excessive fluid retention or an unstable blood pressure which suggest that a minor abnormality may be present.

Summary

Definite and characteristic changes in renal function as measured by endogenous creatinine and uric acid clearances can be demonstrated in pregnant women with pre-eclampsia and in those with acute toxemia superimposed upon chronic hypertension, those with essential hypertension, and those with unclassified "toxemia," when compared with normal pregnant women. In normal women both the creatinine and uric acid clearances were higher prior to the thirty-second week of pregnancy when glomerular filtration reaches a maximum than they were during the last 8 weeks of the gestation period. In most instances the figures were higher than those considered to be normal for nonpregnant women, irrespective of the period of gestation at the time the test was made. It is necessary to recognize this variation particularly in setting up a standard for the comparison of renal function in abnormal conditions.

The normal fall in the clearances as pregnancy advanced was not observed in patients with essential hypertension unless it was complicated by a superimposed acute process, in which event both the uric acid and the creatinine clearances were reduced simultaneously. The changes in the latter patients were almost identical with those observed in women with pre-

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eclampsia and on the basis of the clearance studies alone it was impossible to differentiate one from the other. The reduction in renal function tended to be greater the more severe the toxemia but this relationship did not always hold true because there was considerable overlapping of results.

The clearance studies of both uric acid and creatinine provided a far more accurate evaluation of the excretion of the materials than did the blood levels. Abnormally high blood creatinine levels were seldom observed and those of uric acid often were normal even though the clearance was reduced.

Because the changes in the creatinine and the uric acid clearances follow each other so consistently in normal as well as in abnormal patients, it seems likely that the low clearance of uric acid in pre-eclampsia, which often is attributed to a selective increased tubular reabsorption, actually represents a decreased glomerular filtration of the material.

Single clearance studies are of little value in either diagnosis or prognosis but relative changes in the creatinine and uric acid excretion usually can be observed as the severity of toxemia progresses and may be helpful, when considered in relation to the clinical signs, in determining treatment. A single uric acid or creatinine clearance study will not often indicate those who will develop pre-eclampsia, but a progressive fall which is greater than the normal and which antedates positive clinical signs can be detected with serial tests and may be useful in prognosticating the development of pre-eclampsia.

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THE USE OF LONG-ACTING CURARINE IN OBSTETRICS A Preliminary Report

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O^{UR} interest in the obstetrical potentialities of Tubadil, long-acting tubocurarine in repository form, stemmed from the reports¹⁻³ indicating its role as an anal sphineter, perianal, and perineal muscle relaxant which thus relieved the pain of hemorrhoidectomy. It was also reported to be useful and safe in abdominal surgery,⁴ traumatic injuries,^{5, 6} orthopedic surgery,⁷ acute low back strain,^{8, 9} in the control of muscle spasm in tetanus,^{10, 11} and in acute poliomyelitis.¹²

Over the past fifteen years the use of aqueous tubocurarine and other synthetic muscle relaxants in general abdominal surgery has become well established. This is based on the pharmacological action of tubocurarine in blocking transmission of nerve impulse to skeletal muscle at or near the somatic myoneural junction. This blocking action of tubocurarine on the somatic nerves to skeletal muscle is analagous to that of atropine on the parasympathetic nerves supplying smooth muscle. Tubocurarine is a relaxant of skeletal muscle, reducing its tone or contractile power by specific peripheral effect. Aqueous tubocurarine and the synthetic curariform drugs have also been employed for cesarean sections as well as for vaginal deliveries. 13-19

In the latter, these relaxant drugs have been administered toward the end of the second stage of labor to facilitate the birth of the head by relaxing the perineum while the patient was under anesthesia, and have been found to be safe for both mother and child. Aqueous curare and the curariform drugs, however, are marked by an action, which though worth while in the production of relaxation of the perineal floor at the actual time of delivery, fails to offer similar advantages throughout all stages of labor and the early puerperium.

The desirability of prolonged relaxant effect is apparent in the needs of both the parturient and postpartum patient. The woman in active labor might conceivably deliver sooner and with less trauma to pelvic and vaginal tissues as well as to the presenting part if the perineal musculature could be relaxed so as not to respond to this trauma with protective reflex spasm. The bulbocavernosus (sphincter vaginae) is a skeletal muscle surrounding the vaginal orifice; when it contracts reflexly or voluntarily it narrows the orifice of the vagina.

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In surgery, aqueous tubocurarine is employed deliberately to produce paralysis of skeletal muscles in order to facilitate the accomplishment of the

operative procedure. In obstetrics, however, one seeks a modification of this physiopharmacological action, that is, relaxation without paralysis, a state of functional denervation. With the production of such a controlled state, injury to the anus and rectum might be prevented. The frequency and depth of episiotomies might be reduced, the application of forceps and forceps extraction carried out with less traction and trauma, while spontaneous delivery might be expedited. The need to maintain moderate relaxation of perineal muscles traumatized by delivery is no less important in the postpartum care of the patient, since it has been demonstrated that as muscle spasm is relaxed its painful component is also relieved and the vicious cycle of fear-pain-spasm is broken.

Pharmacology of Tubadil

Tubadil is a slowly absorbed form of d-tubocurarine chloride in a menstruum with a melting point of 38° C. Each cubic centimeter of Tubadil represents d-tubocurarine chloride pentahydrate, 25 mg.; oxycholesterol derivatives, 312 mg.; white wax, 20 mg.; chlorobutanol anhydrous, 5 mg.; and peanut oil, 562 mg. (0.61 c.c.). We selected Tubadil because previous experience¹⁻¹² had shown it to produce no local irritation and to be free from the production of allergic reactions; also because the d-tubocurarine chloride was of an extremely high degree of purity (99.95 plus per cent), and therefore there were no unpredictable side reactions due to impurities present in the alkaloid. The muscle-relaxing effect is apparent in 45 minutes and continues for from 12 to 24 hours or more.

Certain measures should be followed to obtain the maximum usefulness of the drug. Those who use any curare preparation should be familiar with the signs and symptoms of overcurarization and with measures to combat this immediately, although in our experience with Tubadil excessive curare effects are of a theoretical nature. In the event of annoying side reactions, such as heaviness of the eyelids, diplopia, or marked general muscle relaxation, the intramuscular injection of 0.5 to 1 c.e. of neostigmine (1:2,000) is effective, or the intravenous injection of 1 c.c. Tensilon. Tubadil must not be used in patients even suspected of having myasthenia gravis. The dose must be accurately measured before being administered. The drug is administered intra-muscularly with a 19 gauge needle, 2 inches long, into the upper outer quadrant of the buttocks only. The vial is warmed before use to liquefy the suspending medium. The total dose is given in the one site. The patient is advised to refrain from excessive muscular activity for several hours after the administration of the drug. External heat must not be applied to the site of injection as this would increase the absorption rate, and the site must not be massaged for the same reason. If it is proposed to use the drug over an extended period, it should not be repeated in less than 24 hours.

Clinical experience has shown Tubadil to be safe except for transient diplopia and decided relaxation. The objective explanation for this clinical observation is found in a study of plasma levels following intravenous administration of aqueous tubocurarine as compared to intramuscular Tubadil. Pittinger, Morris, and Cullen²⁰ reported that intravenous administration of aqueous tubocurarine produced a typical spike curve in the first few minutes after injection. Of significance is their observation that spontaneous intercostal activity did not resume in any subject while the plasma concentration of tubocurarine was 3 µg or greater. This is in agreement with an earlier observation by Mahfouz,²¹ who found by a biological method that a level of 4 µg was required to produce diaphragmatic paralysis.

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Moyers²² recently reported that when Tubadil was injected in human beings at the beginning of an operation, at a dosage of 0.5 mg. of tubocurarine per pound of body weight (top dose 90 mg. tubocurarine or 3.6 c.c. of Tubadil), plasma levels were in the range of 1 μ g. per cubic centimeter at any time following administration. The rise was slower but more prolonged, as expected.

The use of tubocurarine in aqueous solutions for relief of labor pain is restricted because the effects are of rapidly varying intensity and short duration, so that frequent injections are required. The sharp peak effect of each injection enhances the possibility of respiratory paralysis and thus necessitates close and continuous supervision. These shortcomings are overcome by the use of a highly purified form of the drug in a medium which results in a slow, but more even, sustained effect. Plasma concentrations following Tubadil change gradually and remain well below levels which are associated with paralysis of the intercostal muscles. Thus the usual dose of aqueous tubocurarine given intravenously is effective for about 20 to 30 minutes, while the slow-release-menstruum preparation provides an effect for at least 8 hours, that is, throughout the interval of greatest labor pain.

In the dosages of Syncurine used, Jewell¹⁹ demonstrated that this curarelike drug does not cross the placental barrier and therefore exerts no effect on the baby. Pittinger and associates,¹⁸ in a study of vaginal deliveries conducted during profound curarization, demonstrated that there was no laboratory or clinical evidence of placental transmission to the baby.

Procedure and Dosage

We are currently engaged in investigating the usefulness of Tubadil during active labor and following delivery along the lines mentioned above. To date we have employed Tubadil in 100 patients, 50 of whom were service patients at Meadowbrook Hospital, and 50 private patients delivered by the author.

Our schedule calls for the intragluteal injection of 1.5 to 2 c.c. Tubadil once the diagnosis of active labor is established. The 2 c.c. dose is used at the present time for patients whose nonpregnant weight is more than 120 pounds.

Results

The attempt was made to evaluate the action of Tubadil during labor, delivery, and immediately after delivery by two independent groups of investigators using previous clinical experience as a control:

The duration of the first stage of labor was not markedly affected. The contractions and rapidity of cervical dilatation are not affected since uterine musculature is nonstriated and curare acts at the myoneural junction of striated muscle. With the dosages employed, the voluntary contractions of the abdominal muscles during the second stage of labor were not inhibited; 40 per cent of the deliveries were spontaneous.

Rectal examination was facilitated and made practically painless in 90 per cent of the parturients. Perineal pain resulting from distention by the presenting part either was not present or was only moderate in over two-thirds of the patients. Perineal distention is the most painful episode in labor and its relief in such a large percentage of the patients only lightly sedated allows the second stage to progress toward an easy outlet forceps or spontaneous delivery without further analgesic medication.

Perineal Relaxation.—To evaluate more objectively the effect of Tubadil on the voluntary muscles of the perineum a small group of patients awaiting gynecological surgery were tested with a Kegel perineometer before and after administration of Tubadil. These patients showed a 30 to 50 per cent decrease in voluntary vaginal muscular control. By manual examination, we considered the perineum to be unusually relaxed in 92 per cent of the parturient patients treated with repository tubocurarine. This degree of relaxation was not sufficient, however, to obviate the need for episiotomy in all cases; 74 per cent of the patients in this study required episiotomy but the extent and depth of the incision were reduced in most of them. The episiotomy extended to the vaginal sulcus in three. There were no third-degree perineal lacerations.

Forceps.—Forceps were used in 56 per cent of the cases. Forceps application and extraction seemed to be facilitated in all but one of the forceps deliveries. There were two breech presentations in the series: one was delivered by the Mauriceau maneuver and one by forceps to the aftercoming head. Both deliveries seemed to be facilitated by the perineal relaxation. The incidence of persistent occipitoposterior and transverse in this series was only 5 per cent. This figure is in accord with the usual incidence and is evidence that the relaxation produced is not of such magnitude as to result in persistent malpresentations.

Newborn.—The respiratory state of the newborn infants was satisfactory in 90 per cent. In the 10 per cent of the infants whose respirations were delayed, the effect was probably not due to curare because once respirations were established the chest muscles functioned without weakness.

Postpartum Results.—In no case was the action of the oxytocic (Pituitrin or ergotrate) adversely affected. The need for postpartum catheterization was reduced to a very low incidence, probably due to prevention of spasm of the urethral sphineter. One patient, who had experienced puerperal urinary retention for one week after her first difficult delivery, voided spontaneously soon after her second equally difficult confinement. The common complaint of postpartum perineal pain when reacting from anesthesia was absent throughout the series. Backache, a very common puerperal disability, probably originating when a resisting patient is put up in stirrups in lithotomy position for delivery, was noticeably absent during the hospital confinement of our patients.

Comment

The two events which seem to disturb the moderately and safely sedated labor patient are the pain of rectal examinations and the stretching pain caused by the presenting part on the perineum.

It is a known fact that many rectal disturbances in women originate after pregnancy, and in some fissures in ano may be produced by rectal examination. Hemorrhoids and prolapse of the rectal mucosa may be aggravated by the straining of labor against sphincter spasm. Except in patients given early regional nerve blocks, the perineal stage is the most painful experience in labor, even in patients sedated or conditioned by natural childbirth technique. This pain is due to muscle trauma with resulting spasm. If the painful component of spasm were abolished or diminished by functional denervation, the most painful episodes in parturition prior to actual delivery could be ameliorated and the way paved for delivery under any chosen technique: pudendal, saddle, caudal block, or general anesthesia, or even with no anesthesia at all.

Summary

Our preliminary observations in this small group of patients confirm the relaxant effect of Tubadil, which is generally apparent in 45 minutes and is indicated by the ease and diminished pain of rectal examination. The duration of relaxant effect is apparent for 8 to 12 hours. The majority of patients given Tubadil have shallower and not so extensive episiotomies, easier deliveries, and a remarkably less painful immediate postpartum period. Of significance, too, is the lessened need for postpartum catheterization. A lower plane of general anesthesia is possible when Tubadil is used. We have observed no ill effects in either mother or child which could be attributed to Tubadil.

Our investigations are being continued and will form the subject of a more comprehensive report at a later date.

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ECTOPIC ENDOMETRIUM IN ABDOMINAL SCARS FOLLOWING CESAREAN SECTION

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E NDOMETRIOSIS was first described by Russell in 1899. Voluminous reports have since been written before and after the classical dissertation by Sampson in 1921 in which he described the clinical as well as the pathological changes in this entity.

Our review is intended not only to ascertain the number of published cases of postoperative endometriosis which occurred in the abdominal scars following cesarean section or to focus attention on the varied pathogenetic theories, but also to warn doctors as to the frequency of this condition, which is much greater than one would suspect.

TABLE I. INCIDENCE OF ECTOPIC ENDOMETRIUM IN VARIOUS LOCATIONS REPORTED BY VARIOUS AUTHORS

JENKINSON AND BROWN	KING	KEENE	CLARK	NOVAK*
Ovary Rectosigmoid Fallopian tubes and broad ligament Peritoneum of cul-de- sac Uterosacral ligaments Peritoneum of urinary bladder Intraperitoneal round ligament Umbilicus Laparotomy scar Appendix		Ovary Umbilicus Laparotomy scar Tube Peritoneum Inguinal canal Sigmoid	Ovary Sigmoid Inguinal canal Laparotomy scar Peritoneum Tube Umbilicus	Ovary Uterine ligaments Rectovaginal septum Pelvic peritoneum Umbilicus Laparotomy scar Hernial sac Appendix Vagina Cervix Tubal stumps Extremities

^{*}Slightly modified.

The order of frequency of development of abdominal endometriosis in various sites varies with different authors as presented in Table I. Endometriosis following term or near-term cesarean section is found in about $1\frac{1}{2}$ cases per thousand or about one-fifteenth as often as endometriosis in scars from other uterine abdominal operations. The statistics given by various authors are different and quite difficult to interpret. As shown in Table II, Hepp failed to find an instance in 23 cases, whereas Fitzgibbons reported 2 cases of ectopic endometriosis in abdominal scars, one in post-cesarean section scar.

The symptomatology is very varied. Harbitz stated that the dislocation of endometrial tissue into laparotomy scars appears with clinical signs and symptoms only in women during the period of sexual maturity. However, in another passage Harbitz contradicted this statement by reporting the case of a 12-year-old girl who had never menstruated, yet developed endometriosis. The most frequent location of ectopic endometrium in the abdominal wall is in the midline from the umbilicus to the pubic bone. In one-third of the cases, the symptoms were found within the first year after operation. There are a few cases reported, however, in which symptoms were present only several years after the abdominal intervention. There are 38 reported cases of endometrial implant in scars following cesarean section at term or near term (Table III). We feel certain, however, that there should be many more cases reported, as some of the European countries were not included and most of the reports were obtained from Scandinavian, German, English, and American literature. We might also state that there were 14 cases reported by Harbitz, of which 2 were post-cesarean section scars with endometriosis, 12 cases were called small cesarean sections or sterilization operations. These 12 were deleted from our statistics.

TABLE II. INCIDENCE OF ECTOPIC ENDOMETRIUM IN SCARS FOLLOWING CESAREAN SECTION

AUTHORS	YEAR	TOTAL NUMBER OF CASES	ECTOR	OF CASES OF PIC ENDO- RIUM IN FOMY SCARS	ECTOPIC IN SCA	R OF CASES OF ENDOMETRIUM RS FOLLOWING EAN SECTION
Heaney	1925	NS*	29†		9†	(30.03%);
Keene	1925	113	1	(0.88%)	NS	
Hosoi and Meeker	1928	NS	87†		13†	(14.89%)‡
Haselhorst and Otto	1930	NS	27		1	(3.70%)‡
Harbitz	1934	NS	193†		14†	(7.25%)‡
Masson and Marble	1935	576	10	(1.73%)	2	(20.00%)‡
Clark	1939	29	2	(6.89%)	NS	
Fallas and Rosenblum	1940	260	3	(1.15%)	NS	
Wyrens and Randall	1942	NS	31†		4†	(1.29%);
Jenkinson and Brown	1943	117	3	(2.56%)	NS	
Fitzgibbons	1951	182	2	(1.09%)	1	(50.00%)‡
Attygalle	1952	109	1	(0.91%)	NS	
Hepp	1952	271	23	(0.84%)	0	

*Not specified.

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†Including the previous literature.

tPercentage of ectopic endometrium in scars following cesarean section.

Clinically, the ectopic endometrial growth exhibits swelling which is usually painful, the degree of pain varying according to the different authors as seen in Table III. The pain radiates in the groin and there is swelling with tenderness. As the pain decreases, there may be external bleeding and formation of fistulous tracts with very little discomfort. When the drainage is free, pain ceases. In or below the scars, one usually finds a tumor mass made up of glands with columnar or cuboidal epithelium; some of the cells are ciliated which is in keeping with Sampson's theory, who found in many cases that endometriosis was due to aberrant tubal mucosa. The glands may contain fibrin, cellular debris, partially degenerated red blood cells. The stroma surrounding the glands is of the usual cytogenic variety of the uterine mucosa which is infiltrated by lymphocytes and plasma cells; sometimes hemosiderin is found in the stromal

TABLE III. ECTOPIC ENDOMETRIUM IN SCARS FOLLOWING CESAREAN SECTION

AUTHORS	YEAR	AGE	PREVIOUS PREGNANCIES AND OPERATIONS	OCCURRENCE AFTER LATE OPERATION	LOCATION OF THE GROWTH IN THE SCAR	SYMPTOMATOLOGY	EFFECT OF THE MENSES
Meyer	1903				and described the second of th		
Meyer	1903						
Von Franqué	1916	NS*	KS	1 year	Lower corner	Symptomless	Symptomless
Cullen and Burnam	1922						
Cullen and Burnam	1922						
Sampson and Mallory	1922						
Sampson and Mallory	1922					,	
Abbott	1924	34	1 pregnancy	3½ years	Lump in the middle third of scar	Increasing in size, tenderness	NS
Abbott	1924	37	NS	7½ years	Tumor of the upper part above navel	NS	Slight soreness
Sampson	1924	30	1 cesarean section	Few weeks	NS	Gradual increase in size Increase in size	Increase in size
Sampson	1924	37	NS	7½years	Upper part	Symptomless	Tenderness
Danforth	1925	20	1 pregnancy	2 years	Lump in lower third	Hard, tender mass	Symptomless
Danforth	1925	NS	NS	1 year	NS	NS	NS
Heaney	1925	35	NS	1 year	Lump in upper end	Tender swelling fistula	Swelling
Luetzenkirchen	1925	NS	NS	NS	NS		NS
Berkeley	1926	30	1 pregnancy	3 years	Lump in lower end	Gradual increase in size, painful	More pain
Bonney	1926						
Schwartz	1927	28	NS	2 years	Upper end	Sensitiveness	NS
German	1928	58	NS	4½ years	1 nodule in scar 1 in stitches scar	NS	Painful swelling

German	1928	36	NS	NS	N. N.	NS	NS
Rieck	1928	NS	NS	14 years	Left corner	Fistula	Bleeding
Williams	1929	35	2 cesarean sections	7 years	Upper end	Pain	Symptomless
Haselhorst and Otto	1930						
Schmechel	1930	NS	NS	3 years	NS	NS	NS
Edwards	1932	99	3 pregnancies 2 cesarean sections	10 months	Upper end	Symptomless	Bleeding
Mengert	1932	31	2 pregnancies 2 cesarean sections	3 years	Lump upper angle	Increasing in size, pain Swelling, more pain	a Swelling, more pain
Martin, Michon and Pigeaud	1933	37	2 cesarean sections	NS	Upper end	Fistula	Bleeding
Harbitz	1934	34	2 pregnancies 1 recurrence	1 year	Lower corner	Tenderness, disappearance at pregnancy, reappearance after	Severe pain
Harbitz	1934	87	2 cesarean sections	5 years	Lump in lower end	Symptomless	Symptomless
Masson and Marble	1935						
Masson and Marble	1935						
Stanley	1937						
Codman	1939						
Novak	1940						
Wyrens and Randall	1942						
Wyrens and Randall	1942						
Grimes	1950	26	1 pregnancy	2 years	Upper part	Slight tenderness	Symptomless
Fitzgibbons	1951						

structures or in macrophages. In other cases, there is a foreign-body type of giant-cell reaction, especially surrounding the cotton thread which was used in the previous operation. The glands sometimes proliferate and follow the usual menstrual cycle. In cases of pregnancy, decidual reaction in the ectopic endometrium was reported during extrauterine as well as uterine pregnancy.



Fig. 1.—Case 1. Gross appearance of the surgical specimen. Note the scar of the skin (upper arrow) with the lump in the lower portion and the nodule in the subcutaneous tissue (lower arrow).



Fig. 2.—Case 1. Islet of endometrial tissue surrounded by a cytogenous stroma, scattered throughout a fibrous hyalinized tissue. (Hematoxylin and eosin. $\times 120$.)

CASE 1.—B. M., a 41-year-old woman, was admitted to Columbus Hospital in November, 1953, on Dr. Meyer's service. The patient had had a prolonged labor necessitating cesarean section 11½ years before the present admission. A drainage tube was left in the abdomen about one month and the wound healed without drainage or bleeding after removal of the tube. Symptoms of vague pulling and numbness occurred the year before admission and she noted a lump in the incision which was painful, produced nausea and vomiting, and was relieved by medication and a heat pad. The frog test was negative. During the last two periods, the patient was bleeding from the mass; bleeding ceased after menstruations which were regular. Examination of the lower abdomen revealed a tenderness in the midline below the umbilicus at the junction between the middle and lower thirds and in the former

cesarean section scar a hard lump was palpable. No other aberrant masses were found. Clinical diagnosis was ventral hernia with ectopic endometrium in the abdominal wall. A complete laboratory workup was not contributory.

At the time of operation, a nodular mass of firm tissue was found beneath the depressed area in the lower portion of the abdominal scar. The node was mottled reddish white, external to the fascia, and was excised in toto. The specimen consisted of a piece of tissue measuring 12 by 6 by 5 cm. It was partially covered by pigmented skin and consisted chiefly of subcutaneous tissue (Fig. 1). A nodular mass was found in the subcutaneous tissue measuring 3 by 2 by 2 cm. and extending to the derma propria. The mass was hard and grayish white with several pinhead-sized central red cores. Microscopic section revealed the stroma to consist of a hyalinized scarred connective tissue containing islands of endometrial glands (Fig. 2), which were surrounded by a coating of cytogenic tissue; these were fused with one another, thus forming islets. The glands were inactive; some of them were dilated and cystic. In one portion, the tissue was lined by skin which contained lanugo hair and sebaceous glands. There were many groups of macrophages loaded with brown pigment of hematic derivation. Pathological diagnosis was: Endometriosis in abdominal scar after cesarean section.



Fig. 3.—Case 2. Group of inactive endometrial glands in the subcutaneous tissue. (Hematoxylin and eosin. $\times 300$; reduced $\frac{1}{4}$.)

Case 2.—G. H., a woman aged 50, was admitted to Frank Cuneo Memorial Hospital in August, 1954. The patient had had a cesarean section 13 years before the present admission. The wound healed without drainage or bleeding. One year before the present admission, the patient began to complain of pain in the hypogastric region which was vague, irregular, and without apparent cause, although it seemed to be more frequent 3 to 4 days before and during the menstruation. Examination of the abdomen revealed a midline scar extending from the umbilicus to the pubic symphysis, the result of the previous cesarean section; 1½ inches below the umbilicus in the scar, a mass the size of an egg was found, which was free and

movable below the skin and painful on pressure. A clinical diagnosis was made of umbilical hernia with incarcerated omentum. Complete laboratory workup was not contributory.

At operation, a tumor mass was found in the subcutaneous tissue which was fixed to the fascia of the rectus muscles; no connection between the mass and the peritoneal cavity was found and the mass was excised in toto. The specimen consisted of a piece of the tissue measuring 13 by 7 by 5 cm., one surface of which was covered by pigmented skin presenting an old surgical scar; 1½ cm. below the umbilicus and about 1 cm. into the depth of the scar tissue, a tumor mass was found which measured 3 by 3½ by 3 cm. located in the subcutaneous tissue only. Its consistency was hard and its color grayish white with a few small, apparently hemorrhagic central areas.

The microscopic examination showed the nodule to be located in the subcutaneous tissue and to consist of several areas containing endometrial glands surrounded by a coat of cytogenous stroma (Fig. 3). As in the previous case, the glands were inactive and some of them were dilated and cystic. The stroma was cellular with a mild infiltration of chronic inflammatory cells, mainly plasma cells. Some of the previously described areas showed a myxomatous degeneration.

The pathological diagnosis was: endometriosis in abdominal scar (post cesarean section).

Comment

The cases presented can readily be explained either by Sampson's implantation theory or by Robert Meyer's celomic metaplastic serosa-epithelium hypothesis.

Against the Sampson theory is the fact that the literature contains a case of a 12-year-old girl who had endometriosis long before the menarche began (Harbitz); second, the finding of endometrial implants on the arm and leg in other cases (Novak) makes it difficult to ascribe the Sampson mechanism to all cases of endometriosis unless one is cognizant of the fact that these implants have potent histolytic properties and are able to travel to and metastasize in distant foci (Harbitz).

In favor of the Sampson theory are the facts that: (a) Endometrial implants have been proved to be viable in human (Schmidt, Haselhorst, Caffier) and animal experiments (Manzi, Gleave, Jacobsen). (b) Viable implants have been successfully transplanted in scars in the chest (Harbitz) and in the eye (Neumann); in the pleura they have migrated and even invaded the ribs. (c) Metastasis by way of lymph channels is recognized by Sampson, R. Meyer, Dawidowsky, Halban, and W. Schiller. This could account for distant dissemination, retrograde or via the vascular tree in the rare cases of implantation in limbs. (d) Barriers may be traversed because of the histolytic activity of these particles and in other cases of an intercommunicating system, in a way similar to that described by Batson in cancer of the prostate with cerebral metastases without lung involvement; paradoxical embolism may be a cause in such a rare event, as in the case reported. Breaking through the pulmonary arteriovenous barrier by the slow histolytic property of endometrial particles may be another explanation. (e) Harbitz has shown experimentally that transplants were not influenced by the time they were taken in the menstrual cycle or even if placental tissue was used. The same holds true for changes encountered from variation of

hormonal balance at the menarche and menopause. This tends to negate the hormonal influence per se. Gruenwald's hypothesis follows Cohnheim's theory and is hard to bridge over in the light of known facts.

This brings us to Sampson's theory with its multiple elaborations. Sampson insists that endometriosis results from implantation of differentiated Müllerian tissue, endometrial or endosalpingeal tissue which was regurgitated as small particles from the Fallopian tubes, some of which may have entered via the lymph channels and gone on to proliferate.

Robert Meyer raised what he himself called the theory of "adeno serositis," which means transformation of peritoneal endothelia, sensitized by chronic inflammation into columnar cells, forming glandular structures duplicating endometrium, but he admits that there is also the possibility of implantation. However, R. Meyer describes inflammation as the stimulating agent, while Lauche, Novak, and others believe the mechanism to be on a hormonal basis.

From a review of the literature and our experience in cases of extraperitoneal implants seen and studied, with the only exception of the case of the 12-year-old girl reported by Harbitz, we agree with the Sampson theory. To explain endometriosis of the arm and leg, the implant particles could cross the lung barrier as an embolus paradoxicus or because of their high histolytic activity, as R. Meyer and Kitai have emphasized. Lung implants have not been studied.

Clinical and experimental work is sufficient to explain the endometriosis of the genital organs and the intraperitoneal endometriosis even admitted by the opponents of the Sampson school. The Sampson theory received support in both human and animal experiments by such notable workers as Te Linde and Scott, Keettel and Stein, Jacobsen, Harbitz, Teilum and Madsen, and many others. The fact that some abdominal implants extended from the scar to the uterus, plus the overwhelming occurrence of these implants after surgical intervention on the genitals, supports the Sampson view.

Summary

- 1. Two cases of endometrial implantation in abdominal scar after cesarean section are presented.
- 2. The various theories to explain the origin of the ectopic endometrium are evaluated and supplemented.
- 3. The literature is brought up to date and corrected for the term cesarean section endometriosis.

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INCIDENCE OF HEMOLYTIC DISEASE OF THE NEWBORN DUE TO A OR B INCOMPATIBILITY*†

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H EMOLYTIC disease of the newborn infant arising from Rh incompatibility is generally well understood and adequately managed. Uncommon instances of hemolytic disease result from incompatibility with respect to rarely antigenic properties of the Rh-Hr system or from anti-Kell, anti-Cellano, anti-Duffy (Fyb), anti-S, anti-s, or other antibodies which are also rare. Besides these two broad etiological categories of hemolytic disease, however, there are a substantial number of newborn infants who show clinical signs of hemolytic disease in which the difficulty seems to arise from incompatibility with respect to A or B.

Halbrecht² showed that the cardinal clinical feature of hemolytic disease resulting from A or B incompatibility is the early onset of jaundice in the newborn infant. He showed that jaundice which becomes manifest within the first twenty-four hours of life is almost never physiologic icterus of the newborn. It has been shown that the hemolytic disease due to A or B incompatibility occurs as often in the first as in subsequent pregnancies and may lead to kernicterus or to stillbirth. Male and female infants are affected with equal frequency. The disease is generally less severe than erythroblastosis fetalis due to Rh incompatibility and does not generally become more severe in subsequent infants than in the first affected infant in a given family. B incompatibility is generally more severe than A incompatibility.

The importance of A and B incompatibility as a potential cause of kernicterus may be in some measure inferred from the following data: Over a period of 18 months, of 13 children referred to the Cerebral Palsy Clinic of St. Christopher's Hospital for Children with clinical findings consistent with cerebral damage due to kernicterus and with histories of neonatal jaundice, it was established that the cause of kernicterus was unsuspected Rh or Hr incompatibility in 7 instances and A or B incompatibility in 5 instances. One child appeared to have developed kernicterus in the neonatal period as a result of hereditary spherocytosis.

The presence in most adults of natural antibodies against A or B was responsible for early confusion in the recognition of hemolytic disease due to A or B incompatibility.

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Witebsky's studies have tended to resolve this dilemma by demonstrating that the occurrence of hemolytic disease due to A or B does not correlate with the titer of "natural" anti-A or anti-B but with the presence in the involved mother of a second kind of anti-A or anti-B agglutinin which differs from "natural" anti-A or anti-B in that it is not active against red cells suspended in normal saline solution and in that it is highly resistant to neutralization by the A and B blood group-specific polysaccharide substances. Other observers have pointed out that hemolytic disease due to A and B incompatibility is associated with the presence of hemolytic anti-A or anti-B maternal serum, with spherocytosis, and with increased fragility of the affected infants' red blood cells.^{4,5}

The incidence of hemolytic disease due to A or B incompatibility appeared from the observations of Halbrecht to be about 0.6 per cent. Hsia and Gellis⁶ found it is about 1 per cent of 1,255 consecutive deliveries. It has been our endeavor to extend observations regarding the incidence of illness due to A and B and to attempt anticipatory diagnosis before onset of clinical illness.

At Abington Memorial Hospital since 1953 and at Temple University Hospital since 1952, careful and continuous watch has been kept in the newborn nurseries for the early onset of icterus in the newborn infant. Nurses, interns, and residents have been alerted to the importance of recognition of early icterus and prompt diagnostic appraisal. In each institution, the period from January through June, 1954, has been selected for investigation of the incidence of A or B incompatibility. In addition, at Abington Memorial Hospital, for a six months' period, an attempt was made to use a routine screening test for possible hemolytic disease due to A or B incompatibility. The test consisted of suspension of red blood cells from cord blood in a dilute solution of LePage's glue, in which it was hoped cells coated with the antibody of hemolytic disease would routinely display spontaneous agglutination. The results of these studies and two illustrative cases are presented.

Methods

Detection of Early Onset of Icterus.—This has been facilitated in the newborn nurseries of Abington Memorial Hospital and Temple University Hospital by the practice of "jaundice rounds" with each change of nursing personnel at about 8 hour intervals. When the age of an icteric infant was noted to be less than 24 to 36 hours, immediate notification of the responsible medical officer was made and steps were taken to establish the probable etiology of the icterus. Laboratory investigations included grouping and typing of parents' and infant's bloods, the Coombs test on infant's cells, the "glue test" on infant's cells (described in the following paragraph), and a search for "immune" anti-A or anti-B in maternal serum. Hemoglobin and bilirubin levels were determined in infant's blood. Additional observations were occasionally made as to occurrence of spherocytes in the infant's blood or hemolysins in maternal serum.

The "Glue Test."—This test was performed by suspending infant's cells, taken from clotted blood, in about 2 to 4 per cent suspension in a medium composed of 1 part LePage's Photoengraving Glue to 9 parts of physiologic saline solution. The suspension of cells is incubated for 5 to 20 minutes at room temperature and centrifuged lightly before being examined for agglutination. Adequate control suspensions are treated identically.

"Immune" Anti-A and Anti-B Antibodies.—These were detected in maternal serum by a modification of the method described by Witebsky. This consisted of neutralization of maternal serum by A or B specific polysaccharide substance, usually in the ratio of 1.5 parts of a commercial preparation of polysaccharide to 1 part of serum, followed by the demonstration of effective neutralization of "natural" (saline-active) anti-A or anti-B, with persistent activity of "immune" anti-A or anti-B shown by agglutination in the glue solution previously described.

TABLE I. INCIDENCE OF HEMOLYTIC DISEASE, JANUARY-JUNE, 1954

		CASES OF HEMOLYTIC DISEASE		
HOSPITAL	NO. OF DELIVERIES	AS A RESULT OF A OR B INCOMPATIBILITY	AS A RESULT OF Rh INCOMPATIBILITY	
Abington Memorial Hospital	1,275	12	10	
Temple University Hospital	1,397	11	5	
Total	2,672	23	15	

Results

The incidence of hemolytic disease observed at the two hospitals over the six months' period of study is shown in Table I. Those cases due to A or B were found to occur in 0.86 per cent of the infants born during this period. These observations confirm those of others that hemolytic disease due to A and B incompatibility is actually more common than that due to Rh incompatibility. The slightly lower incidence of hemolytic disease due to Rh incompatibility at Temple University Hospital than at Abington Memorial Hospital may reflect the higher percentage of Negroes in the series of the former institution.

At Abington Memorial Hospital the use of the glue test as a screening device for diagnosis of hemolytic disease due to A or B incompatibility proved disappointing. There were both falsely positive and falsely negative reactions which rendered its interpretation uncertain. It remains a valuable confirmatory test of active hemolytic disease but it is prone to too many vagaries to make it helpful as a screening device in a situation where it is anticipated only one test in a hundred will be positive and meaningful.

Exchange transfusions were performed in cases of A or B incompatibility in which it seemed necessary to take measures to control the level of serum bilirubin. The following case histories are of interest. The first is typical; the second unusual in that kernicterus had been the consequence of A immunization in a previous sibling.

CASE 1.—Mrs. S. had no history of a sensitizing experience prior to her first pregnancy. Her first child, born in 1952, was markedly interior during the neonatal period. Recovery was complete; no treatment was given. A second infant, born May 5, 1954, was found to be jaundiced at the age of 24 hours. The infant was shown to be group A,

the mother group O. Both were D (Rh₀) positive. The Coombs and glue tests, using the infant's cells, were both weakly positive. The maternal serum contained anti-A anti-body resistant to neutralization to a titer of 1:16 in glue solution. The infant's level of serum bilirubin was 19.9 mg. per cent at 24 hours of age.

An exchange transfusion was carried out 28 hours after delivery, with the use of group O, Rh-positive blood shown to be compatible with the maternal serum. The infant's level of serum bilirubin was 6.4 mg. per cent at the end of the procedure, 16.2 mg. per cent 18 hours later and 9.0 mg. per cent by the fourth day of life. The icterus cleared rapidly and the infant remained well.

CASE 2.—Mrs. T. received an injection of horse serum in the treatment of poliomyelitis in 1941. (Mollison⁴ has shown that this may sensitize to A.) In 1951 she delivered her first infant, a girl, two weeks before her expected date of confinement. The infant became profoundly jaundiced during the neonatal period. The immediate and subsequent courses have been typical of kernicterus of a moderately severe degree. The presumptive diagnosis of A incompatibility was confirmed by grouping the typing of the infant's and mother's bloods and by demonstration of immune anti-A antibody in maternal serum. It is noteworthy that the maternal anti-A antibody was selectively highly active against the cells of the father and only slightly active against other A cells. There was no activity against O cells.

The mother's second child was born during the present study. At delivery, the cord blood contained spherocytes; the glue test was positive, and the Coombs test was negative. The level of serum bilirubin in the cord blood was 3.2 mg. per cent. Eight hours after birth there was slight icterus and the bilirubin level had reached 6.4 mg. per cent. An exchange transfusion was carried out with group O blood compatible with the maternal serum. The subsequent course of the infant was entirely satisfactory. There was slight icterus, associated with a maximal level of serum bilirubin of 10 mg. per cent.

Comment

It is apparent that hemolytic disease due to A or B incompatibility is common. Although the acute phase is generally milder than is that of Rh incompatibility and it is rarely responsible for stillbirth, kernicterus probably occurs in from 2 to 10 per cent of clinically diagnosable but untreated cases. Since kernicterus can be prevented by prompt and adequate treatment with exchange transfusion of blood, the need for prompt diagnosis and treatment of hemolytic disease due to anti-A or anti-B may be urgent.

TABLE II. LABORATORY AIDS IN DIAGNOSIS OF HEMOLYTIC DISEASE DUE TO A OR B INCOMPATIBILITY AND TO Rh INCOMPATIBILITY

	IN A OR B INCOMPABIBILITY .	IN Rh INCOMPATIBILITY
1. Glue test (infant's cells)	Often positive	Usually positive
2. Coombs test	Seldom positive	Usually positive
3. Demonstration of "immune" antibodies (anti-A and anti-B in maternal serum)	Usual	May coexist
4. Demonstration of hemolytic anti-A or anti-B in serum	Usual	May coexist
5. Spherocytic infant's cells	Usual	Unusual
6. Osmotic fragility	Increased	Normal
 Reticulocytosis, anemia, and normo- blastemia 	Correlated with seversity of hemolytic process	Correlated with severity of hemolytic process

There is no better case finding method at the moment than careful observation of infants during the first 24 to 36 hours of life. The onset of ic-

terus within this time establishes a pediatric emergency, and necessitates appraisal by laboratory techniques to establish its etiology. The tests include blood grouping and typing, hematologic studies, and immediate determination of the level of serum bilirubin. Helpful diagnostic aids are summarized in Table II.

Hemolytic disease due to anti-A or anti-B must be differentiated from Rh or other incompatibilities; from sepsis, toxoplasmosis, cytomegalic inclusion disease, and occasionally from icterus neonatorum, hepatitis, hereditary spherocytosis, and rarer illnesses.

Criteria for an exchange transfusion of blood in hemolytic disease due to A and B incompatibilities are not firmly established at the present time. It seems reasonable, however, to assume that the occurrence of kernicterus is correlated with the rise of serum bilirubin as it is in Rh incompatibilities, and that treatment should be planned to control this elevation. Fresh blood, shown to be compatible with the mother's serum by the indirect Coombs technique, is used for the exchange transfusion. Exchange transfusions are repeated as often as necessary to maintain the level of serum bilirubin below 20 mg. per cent, which seems to be the level below which occurrence of kernicterus is unlikely.

Optimum results of treatment depend on prompt diagnosis and early exchange transfusion. No apology need be made for an occasional unnecessary exchange transfusion. The morbidity and mortality in a properly performed exchange transfusion approach zero, as does the incidence of kernicterus.

In some instances, as in Case 2, the history of kernicterus in a previous child permits anticipation of hemolytic disease due to A or B incompatibility before delivery; there the indications for treatment are similar to those in Rh incompatibility. Any of the following are regarded as compelling indications for an exchange transfusion: history of severe involvement in a previous infant; premature delivery at 2 weeks or more before the calculated date; clinical signs of disease (hepatosplenomegaly, pallor, edema) at birth; cord blood hemoglobin less than 15 Gm. per cent; cord serum bilirubin over 3.5 mg. per cent.

Too little is known of the relationship of the maternal titer of immune anti-A and anti-B antibodies to make them useful as prognostic signs.

A relatively common situation, presented in Case 2, was first called to the attention of one of us (V. C. V.) by Dr. Fred H. Allen, Jr.: The blood of the father of the affected infant may be superior to that of another person of the same blood group so far as measuring reactivity to maternal anti-A or anti-B antibodies is concerned. This screening of the maternal serum for immune anti-A or anti-B antibodies should not be regarded as negative unless the serum has been tested against the red blood cells of the father of the affected infant. The cells of the infant are generally unsatisfactory for this purpose since the A property is relatively underdeveloped in early infancy.

Summary

A and B incompatibilities commonly cause hemolytic disease of the newborn. The incidence in this study was 0.86 per cent of 2,672 newborn infants. The chief clinical features is the early onset of icterus. The chief therapeutic problem is prevention of kernicterus.

Criteria for diagnosis and treatment by exchange transfusion are discussed.

Case finding is the joint problem of the obstetrician, the pediatrician, and the nurse.

Thanks are due to Mr. Russell Fowler and Drs. Norman Kendall and Walter D. Reese for assistance in preparing this material.

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ELIMINATION OF THE USE OF THE POSTPARTUM ENEMA

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THE following report on the almost complete elimination of the postpartum enema was prompted by the continued need for sensible simplification in the management of pregnancy and the puerperium. The routine postpartum enema seemed perhaps needless and somewhat tradition bound. Patients dread receiving it, nurses dislike giving it, and doctors should avoid ordering it, if possible. Banner,¹ who discussed this subject in 1953, spoke also of the growing shortage of nurses. Formerly when ambulation was delayed the bowels no doubt did become sluggish and frequently needed the enema. With the advent of early ambulation, however, phenomena of stasis or congestion, such as phlebitis and the atonic bladder, have nearly disappeared. The next question was, Why not obstipation also?

Method

One hundred consecutive obstetrical patients were handled according to the following plan. On the second postpartum evening the patient was given an ounce of mineral oil and the following morning, if no evacuation had occurred, two ordinary glycerine suppositories were inserted into the rectum. Other reports^{1, 2} on this subject have included the use of a specially medicated suppository. If no bowel movement occurred within an hour, another suppository was inserted. If no bowel movement occurred within several hours, nothing more was done until the following morning when this routine was repeated, but this was necessary in few cases. Obviously in selected cases or if specifically requested by the patient, an enema might be indicated before the procedure was repeated the following day.

Of perhaps great importance is the preliminary psychological preparation of the patient which is carried out during the visit of the obstetrician on the second postpartum day. This involves an explanation to the patient of the objective, namely, a spontaneous bowel movement. At this point the patient usually heartily agrees and then the doctor might well reinforce this point by mentioning the new attitude of nurse and doctor concerning enemas. The doctor then proceeds to explain to the patient that the first bowel movement is not a painful experience and that the sutures do not break with the bearing down normally associated with a bowel movement. It also should be pointed out to the patient why the postparturient often feels as though her "insides are pushing down or falling out of the vagina," and that the muscular action of a bowel movement does not cause "anything to fall out." The importance of this mental conditioning of the patient was evidenced by the occasional occurrence of a spontaneous evacuation in the morning before the suppositories could be inserted.

There were at least two other factors which were felt to contribute to the extremely infrequent need for enemas. These were the free use of fluids and

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the avoidance of rectal examinations during labor. The postpartum patients were encouraged to take fluids freely during the postpartum diaphoretic period. At the same time, they were advised that doing so would not adversely affect breast engorgement while, on the other hand, fluid restriction at this time would not reduce engorgement but would contribute toward constipation. Encouraging increased water intake during pregnancy produced almost uniform regularity and little need for cathartics ante partum.

The second factor was the avoidance of rectal examinations during labor. I have reached the conclusion that the high incidence of transient external hemorrhoids in the early postpartum period was in direct relationship to rectal examinations made during labor. Certainly the presence of this painful condition is not at all conducive to spontaneous evacuation.

For over a year, with few exceptions, private labor patients have been examined only vaginally under a careful technique. This has apparently resulted in a decrease almost to zero of this type of external hemorrhoid. Multiparas on frequent occasions have volunteered the information that they much preferred the vaginal to the rectal examination as experienced during previous labor.

The danger of vaginal examinations during labor has possibly been exaggerated, according to Prystowsky,³ who also quoted a paper of Reis⁴ published in 1924 in which the latter showed that there was an equal incidence of febrile reactions regardless of whether only rectal or only vaginal examinations had been done. Prystowsky even noted that the number of patients who did require postpartum antimicrobial drugs was twice as high in the rectal (21 per cent) as in the vaginal examination group (11 per cent). Postpartum elevation of temperature of 100.4° F. or above was reported by him in 10.3 per cent of patients as compared to an incidence of 8 per cent in this series.

Results

In 88 per cent of the patients in this series a spontaneous bowel movement occurred. This compares with 70 per cent as reported by Banner at the Mayo Clinic. In all cases the patients were thoroughly satisfied with their experi-Among the 12 failures were 6 nurses, all primiparas. The 6 other patients were multiparas, in whose minds possibly the idea of routine postpartum enemas had been too firmly fixed and conditioned. Postpartum febrile reactions were apparently in no way unusual. Perhaps the additional use of a mild laxative such as milk of magnesia (in nonnursing patients) to stimulate bowel motility might further improve the results.

Conclusion

As a result of our experience and that of others, it appears that there is little doubt that the routine postpartum enema can be relegated to infrequent use in postpartum management. The greater degree of success achieved in this group compared with that reported by Banner is felt to be due to: (1) vaginal examinations during labor, (2) encouraging fluids ante and especially post partum, and (3) preliminary psychological preparation.

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Department of Case Reports New Instruments, Etc.

THE GUILLAIN-BARRÉ SYNDROME COMPLICATING THE PUERPERIUM

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IN 1916 Guillain and Barré¹ described a syndrome resulting from an inflammatory process in the brain, spinal cord, posterior roots, and peripheral nerves. They demonstrated the characteristic albuminocytologic dissociation in the spinal fluid, the preponderance of motor weakness over sensory disturbances. Mortality rates vary between 20 and 40 per cent, depending upon the acuteness of the disease and the location of the lesion, i.e., bulbar and upper cord lesions compared with lower cord lesion.

The Guillain-Barré syndrome complicating pregnancy has been reported only once before in the literature.²

Case Report

A 23-year-old white woman was delivered without difficulty of a living full-term male infant on Oct. 13, 1954, after an estimated twenty-one hours of labor. Four hours ante partum the patient was given 0.1 per cent intravenous Pitocin (0.5 c.c. Pitocin in 500 c.c. of 5 per cent glucose in water by intravenous drip (20 to 30 drops per minute), because of rather desultory contractions.

The antepartum course was normal. The total weight gain was nineteen pounds. The serologic test was negative; the patient's blood was found to be AB, Rh positive.

On admission the red blood cells were 5.09 million, white blood cells 7,400, hemoglobin 82 per cent, and the differential count showed 73 per cent polymorphonuclear leukocytes, 59 segmented leukocytes, 14 nonsegmented leukocytes, 24 lymphocytes, and 3 monocytes. The catheterized specimen of urine showed 2 plus albumin and a trace of acetone. The specific gravity was 1.022 and microscopically 2 to 3 white blood cells and 2 to 3 red blood cells were found. Two days later the urine contained 2 plus albumin and 2 plus acetone with many red blood cells and 6 to 7 white blood cells. On the first day post partum the patient developed a unilateral Bell's palsy.

A medical consultant (S. L.) saw the patient and found marked local tenderness to compression over the forearm and calf as well as the thigh areas, bilaterally. A complete left facial paresis of a peripheral type and left palatal palsy and diminished gag reflex with tremor of the extended tongue were noted. There was marked weakness of all extremities to all motion, particularly flexion, which was more marked in the right upper and right lower extremities. There was a patchy paresthesia and hypoesthesia over the right foot and right lower leg with definite decrease in vibratory sensation over the right lower extremity; position sensation was intact. The ankle jerks were hyperactive bilaterally and the knee jerks were hyperactive on the right. Biceps and triceps were hyperactive.

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An immediate lumbar puncture was done which disclosed a normal pressure and normal spinal fluid mechanics with one to two lymphocytes and one polymorphonuclear leukocyte per cubic millimeter. The total protein was just over 100 mg. A smear and culture were negative. A heterophile agglutination test taken on Oct. 29, 1954, was negative.

The patient then had a right peripheral facial paresis. She was treated with a 1,000 mg. of vitamin B₁₂ subcutaneously daily in addition to cortisone, 50 mg. every six hours, and large doses of multivitamins orally and parenterally. She made progressive and distinct improvement during the subsequent two weeks and was discharged on Nov. 11, 1954, with some residual paresthesia of both lower extremities and marked improvement in the motor power of all extremities. She was treated at the Middlesex County Rehabilitation Hospital with marked regression of all her neurological findings. When last seen Nov. 30, 1954, the patient was quite comfortable but still had bilateral facial paralysis.

Summary

A case of infectious neuronitis which developed during the puerperium is presented.

The clinical course and findings, with spinal fluid examination, confirmed the presence of the Guillain-Barré syndrome with a rather classical course.

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REPEAT PRIMARY OVARIAN PREGNANCY

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PRIMARY ovarian pregnancy is rare. Primary ovarian pregnancy recurring twice in the same patient is even rarer. This paper is a report of a patient who had a right ovarian primary pregnancy in 1951 and a second left ovarian primary pregnancy in 1953.

Seventeen cases reported since 1943 have brought the total to 114. The references for these 17 cases are included in the Toplak¹ paper. All these were published in the American Journal of Obstetrics and Gynecology between 1943 and 1947 except 3 which were reported elsewhere. I estimate that 100 to 125 cases of single primary ovarian pregnancy have been reported. Whatever the total number of cases reported, the incidence is low.

Present opinion of primary ovarian pregnancy (Castleton²) favors the theory that the ovum is discharged from the ovary, fertilized in the tube, and then for some unknown reason is discharged into the peritoneal cavity and then implanted in the cortex of the ovary or even in a ruptured follicle. Fertilization and implantation may occur in the tube. The sac could become dislodged to form a secondary implantation in the ovary. Thus to prove a primary ovarian pregnancy the tube must be separate and normal.

Even at operation the precise diagnosis is seldom recognized. At the first operation on our patient we felt that we had removed a ruptured bleeding ovarian cyst. The diagnosis was made by the pathologist, Dr. F. K. Lott, on the microscopic findings. At the second operation two years later we were amazed to find the same pathological picture in the abdomen and by the virtue of our earlier experience with this patient reasoned that this was another ovarian pregnancy in the same woman. Subsequent microscopic examination by Dr. Craig Freeman confirmed our suspicions.

Case Report

Mrs. D. E. S., a 25-year-old gravida ii, para i, had one 4-year-old child. Until Sept. 9, 1951, she was in normal health. After she ate breakfast lower abdominal cramps began. The cramps continued all day. A hot-water bag relieved the patient. All three meals were eaten. The patient stayed in bed all day and slept through the night.

On September 10 the patient was examined. The temperature was 99.2° F., pulse 88, and white blood count 9,550. There was generalized one plus tenderness with no rigidity. The cervix was normal with no bleeding. Bimanual examination failed to reveal a mass.

On September 11 the tenderness centered over McBurney's point. The temperature was 99.4° F., pulse 84, and white blood count 10,500.

On September 13, the patient did not feel any better. The temperature was 98.4° F., pulse 100, and white blood count 10,950. Abdominal findings showed three plus right

lower quadrant tenderness, two plus right rectus rigidity, one plus rebound tenderness. On pelvic examination a mass was felt in the right adnexal area. There was vaginal spotting.

Her general history revealed no serious illnesses and no previous operations. The periods were regular, every 28 days, of 4 days' duration with moderate flow. The last menses was on Aug. 26, 1951. This episode of abdominal discomfort was mid-menstrual.

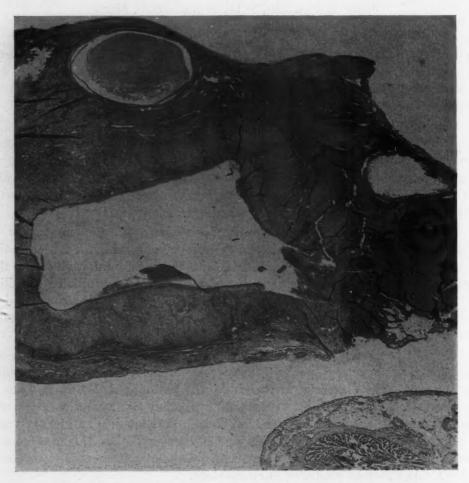


Fig. 1.—Case 1. Macroscopic view of ovarian tissue removed (1951).

On Sept. 13, 1951, a laparotomy was done. The abdominal cavity contained about 500 c.c. of blood. The right ovary had a hemorrhagic ruptured bleeding ovarian cyst. A right salpingo-oophorectomy was performed. The appendix was removed. The uterus, left ovary, and tube were normal. There were no apparent endometrial transplants. A transfusion of 1 pint of blood was given to the patient. Recovery was complete and she was discharged from the hospital on Sept. 21, 1951.

The pathological report was as follows:

Gross: The specimen consisted of the right Fallopian tube and right ovary. The tube measured 5 by 7 cm. The ovary measured 3½ by 3½ by 2 cm. The ovary contained a ruptured corpus luteum. The ovarian surface over this cyst was covered with clotted blood (Fig. 1).



Fig. 2.—Case 1. Medium-power view shows chorionic villi and ovarian tissue relationship.

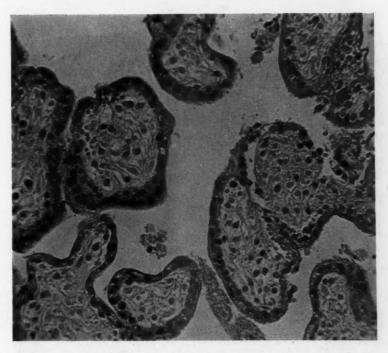


Fig. 3.—Case 1. Microscopic view of ovarian tissue showing the chorionic villi,

Microscopic: The sections through the tube showed normal histology. The sections through the ovary at the point of hemorrhage showed a corpus luteum in the substance of the ovary. On the surface of the ovary there were scattered hemorrhage and numerous chorionic villi. These villi were covered by two distinct layers of cells. No fetal parts were seen. This represented an ectopic pregnancy, ovarian in nature (Figs. 2 and 3).

Twenty-six months later, on Nov. 3, 1953, the same patient gave the following history. The periods had been regular ever since the last operation. The last menses was at the regular expected time, Oct. 16, 1953. The flow continued for four days; then stopped. Two days later the flow resumed with hard cramps and a profuse amount of bleeding.

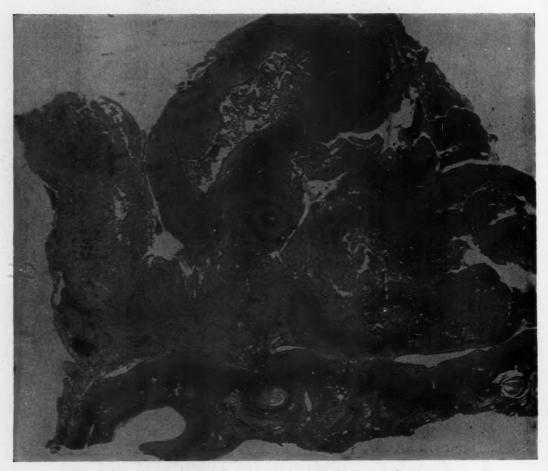


Fig. 4.—Case 2. Macroscopic view of ovarian tissue removed (1953).

Examination of the abdomen showed tenderness in the lower quadrants. There was bleeding from the cervical os. The uterus was small and in normal position. A feeling of a mass was present in the left adnexal area. The white blood count was 5,300.

On November 5, the bleeding stopped. The Friedman report was negative for pregnancy.

On November 11, the flow resumed. The uterus was slightly enlarged. The flow continued from the os accompanied by cramps.

On November 14 a dilatation and curettage was done. The pathological report showed secretory endometrium. However, under anesthesia, pelvic examination disclosed a definite mass in the left adnexal area.



Fig. 5.—Case 2. Medium-power view shows chorionic villi and ovarian tissue relationship.

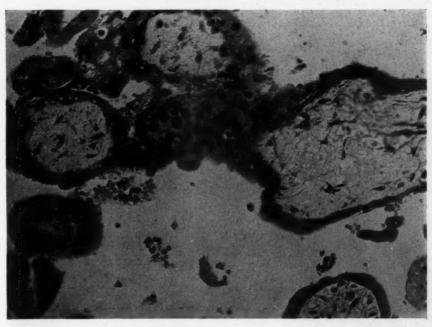


Fig. 6.—Case 2. Microscopic view of ovarian tissue showing the chorionic villi.

On Nov. 16, 1953, a laparotomy was performed and about 500 c.c. of free blood was found in the abdomen. The left ovary was enclosed in a large bloody mass. There was no evidence of endometriosis. A left salpingo-oophorectomy was done. Blood transfusions were given. Recovery was uneventful and the patient was discharged from the hospital Nov. 22, 1953.

The pathological report was as follows:

Gross: The specimen consisted of a left tube and ovary. The ovary measured 41/2 by 4 by 3 cm. The surface of the ovary was covered with a blood clot that measured up to 3 cm. in greatest dimension. The tube appeared normal and measured 6 by 1 cm. (Fig. 4).

Microscopic: The sections through the blood clot at several points showed that the bulk of it was merely hyalinized material. In some areas the clot showed early organization. One section, however, showed numerous chorionic villi which were almost completely hyalinized. The specimen represented an ovarian pregnancy which has become necrotic and undergone partial organization. The section of the tube showed the normal histology (Figs. 5 and 6).

Diagnosis: Left ovarian pregnancy.

Summary

Two primary ovarian pregnancies occurring in the same patient on two separate occasions have been reported.

Both cases conform to the criteria laid down by various authors in past literature, especially the four precepts of Spiegelberg3: normal tube, location of the fetal sac at the site of the ovary, mass connected to the uterus by the uteroovarian ligament, and the presence of chorionic villi.

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GRANULAR-CELL MYOBLASTOMA OF THE LABIUM MAJUS

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GRANULAR-CELL myoblastoma was established as a tumor entity by Abrikossoff in 1926.¹ There have been many case reports and reviews²,³,⁴ in the literature since then, the lesions being found mainly in the skin in various locations of the body as well as on mucous membranes, especially in the tongue. In a review of the literature in 1950, Sadler and Dockerty⁵ were able to find 4 cases of primary vulvar myoblastoma and reported a malignant type of their own. In 1953, Valentine and Thomas⁶ and Watson and Taylor⁻ each reported a case. A recent case has been reported by Reich and associates,⁶ making a total of 8 cases. In 2 of the reported cases, there was a characteristic pseudo-epithelial hyperplasia of the adjacent epithelium. We wish to report another case in which the epithelial hyperplasia was one of the features of the tumor.

L. P. (Case 8062), a 42-year-old white woman, was admitted to St. Joseph's Hospital on Oct. 31, 1954, complaining of a small lump just inside the right labium majus. She stated she had first noted a small pimplelike growth two years previously, which was brought to her attention by an itching sensation of the vulva. It had grown slowly in the two-year period.

The previous medical and surgical history was negative. Menstruation began at the age of 14 and was regular every 28 days and lasted 3 days. She had two children who were delivered normally.

Physical examination showed a healthy-appearing adult woman, not acutely ill. On the right labium majus, there was palpated a circumscribed firm, freely movable, nontender nodule about 1.5 cm. in diameter, just beneath the skin on the posterior portion. The overlying skin was slightly indurated but showed no evidence of ulceration. There were no inguinal glands palpable and no other nodules were present elsewhere on the body.

The blood Wassermann test was negative; the blood count and urine examinations were normal.

The clinical diagnosis was possible fibroma or sebaceous cyst.

The following day the mass was enucleated under Pentothal anesthesia and the patient was discharged on Nov. 3, 1954, with the wound normally healed. There has been no evidence of recurrence to the present time.

Gross pathologic examination of the tumor showed a circumscribed round nodule 2.5 cm. in diameter with a smooth outer surface except for a small elliptical piece of skin which overlay the nodule. It was firm and elastic and cut with some difficulty due to its rubbery consistency. The cut surface was light yellowish gray in color and had the appearance of fibrous connective tissue.

Microscopically the tumor was composed of sheets and groups of large round and polyhedral cells, 25 to 50 microns in diameter with coarsely granular acidophilic and neutrophilic cytoplasm (Fig. 1). The nuclei were large, with one or two nucleoli, and were mostly centrally placed. There were interlacing bands of collagen fibers, separating groups of cells. The margins of the tumor were irregular and no evidence of encapsulation was noted. The overlying epithelium, in contact with the tumor, showed a marked hyperplasia to such a

degree that it resembled frank invasive squamous-cell carcinoma with distinct pearl formation (Fig. 2). The epithelium not in contact with the tumor appeared normal. No evidence of neurogenic tissue was noted in any areas adjacent to the tumor. Fat stains of the tumor were negative.

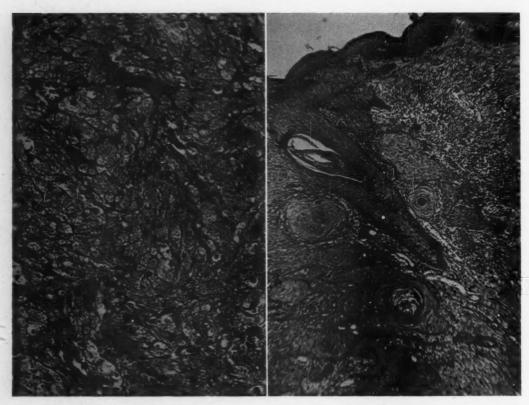


Fig. 1. Fig. 2.

Fig. 1.—Microscopic section showing characteristic cells with granular cytoplasm.

Fig. 2.—Microscopic section showing the pseudoepithelial hyperplasia with invasive tendency and pearl formation.

It has been suggested⁹ that the pseudoepithelial hyperplasia occurring with many of these tumors may be due to the presence of some irritant in the cells of the tumor causing this reaction when the cells come in contact with the epithelium and biochemical or viral studies of the cells may be of value. This reaction does not occur with the ordinary cutaneous leiomyoma. The gross appearance of the skin overlying the tumor in the present case was not indicative of any malignant change occurring, and microscopically there was no evidence of the ordinary inflammatory cellular reaction.

There has been much speculation in the literature regarding the tissue of origin of this tumor but the consensus appears to regard the cells as immature muscle cells. The great majority are innocent tumors and their gross appearance in the location of the vulva usually suggests a simple fibroma or cyst. Simple enucleation in the great majority of cases results in cure with no recurrence.

Summary

A rare tumor of the labium with the microscopic appearance of granularcell myoblastoma has been described, one of the features of which was the marked pseudoepithelial hyperplasia of the overlying epithelium. Simple enucleation with attached skin was performed with no recurrence to the present time. Eight cases of the tumor in this location have been reported up to the present with the great majority apparently of a benign or so-called "uniform" nature.

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CARCINOMA OF THE VESICOVAGINAL SEPTUM*

Case Report

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THE vesicovaginal septum is often involved by carcinoma which has originated in adjacent areas such as the cervix, vagina, or bladder. Rarely one may encounter an instance where the carcinoma seems to be localized to the septum itself. The following case report is an illustration of such a possibility.

H. B. (Case No. 13722), a white, 52-year-old nulliparous widow, was first seen at the American Oncologic Hospital on May 10, 1954. She had been referred to the hospital for management by Dr. Bruce Wolff of Gettysburg, Pennsylvania. Dr. Wolff had first seen the patient on June 15, 1953, because of acute urinary retention. At that time, she stated that she had had nocturia for about one year and difficulty in completely emptying the bladder, some urgency and dribbling for about five weeks. There was no history of hematuria and no history of vaginal bleeding or discharge. The patient had an uneventful menopause about three years previously. Review of systems was not contributory and her past history was essentially negative except for a left salpingo-oophorectomy done in 1928.

Pelvic examination showed a nulliparous outlet, normal urethra, small clean cervix, and a small mobile uterus. Rectal examination was confirmatory. Cystoscopic examination was done and generalized hyperemia, edema, and slight trabeculation of the bladder wall were found. The patient was admitted to the Warner Hospital and treated by urethral dilations and antibiotic therapy. Because of thickening of the vesicovaginal septum, a biopsy of the anterior vaginal wall was done on July 13, 1953, and interpreted as "chronic fibrosing vaginitis." She was seen at intervals and intravenous urography in September, 1953, was considered within normal limits. In April, 1954, because of rigidity beneath the anterior vaginal wall, a biopsy (Fig. 1) was taken and was interpreted as "squamous-cell carcinoma." The patient was then referred to the American Oncologic Hospital.

Pelvic examination at the Oncologic Hospital showed normal external genitals, adequate introitus. The cervix was clean with intact portio; the uterus was mobile. There were no adnexal masses. Beneath the anterior vaginal wall and extending laterally on both sides almost to the posterior vaginal wall, to within 1 to 2 cm. of the external urinary meatus, to within 1 to 2 cm. of the cervix, the tissues were irregular and indurated, but no break through the epithelium could be visualized (Figs. 2 and 3). The posterior vaginal wall was intact and pliable. No regional lymphadenopathy was noted. Slight stenosis of the urethra, moderate trabeculation of the posterior wall of the bladder, and bullous edema of the trigone area were found on cystoscopic examination. Intravenous urography demonstrated normally functioning kidneys and some deformity of the inferior margin of the bladder, particularly in the trigone area, suggesting beginning malignant infiltration. General system survey including chest x-ray was within normal limits. Biopsy taken through the anterior vaginal wall was interpreted as "epidermoid carcinoma, squamous-cell type."

^{*}Presented at a meeting of the Obstetrical Society of Philadelphia, Oct. 7, 1954.

Because of the rather unusual location of the disease, it was considered desirable to treat this patient by means of supervoltage x-ray therapy rather than the conventional 200,000 volt therapy. For this reason, daily therapy was begun on May 24, 1954, and continued through July 15, 1954. The factors of treatment were as follows: 2,000,000 volts; 200 Ma; 70 cm. skin-target distance; 7 mm. lead inherent filter; 300 r daily. Two 18 by 12 cm. fields (right and left posterior) and one irregular anterior pelvic portal (11 by 9 by 6 by 8 cm.) were utilized and a skin total of 3,604 r was delivered to each of the three fields. The total estimated tumor dose was 6,158 r.

During the course of treatment, 1,500 c.c. of blood was given intravenously to the patient because of a leukopenia (1,800 to 3,200 white blood count) which developed while the therapy was being given.

Since completion of treatment, the patient has been seen at intervals. Cystoscopic examination (Sept. 13, 1954) demonstrated the anticipated postradiation hyperemia but no other significant changes. Intravenous urography (Sept. 14, 1954) was considered to be essentially normal. The findings on pelvic examination (Oct. 6, 1954) were noticeably improved and only slight thickening of the vesicovaginal region was found.

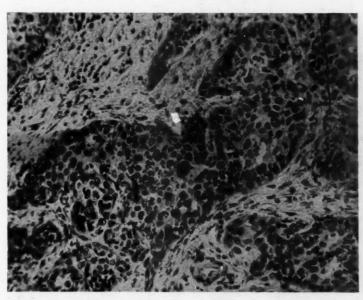


Fig. 1.—Biopsy taken from vesicovaginal septum showing typical infiltrating squamous-cell carcinoma. ($\times 110$; reduced $\frac{1}{2}$.)

Comment

Primary carcinoma of the rectovaginal septum has been reported previously,^{1, 2} as has been an apparent urethrovaginal carcinoma.³

Carcinoma involving the vesicovaginal septum is usually secondary to a primary source in the cervix, vagina, or bladder.

From the embryological aspect, it is conceivable that a primary vesicovaginal carcinoma may arise from urachal or allantoic remnants since these remnants are usually in the midline, but this location would lie rather distant from the usual urachus. The growth may have arisen from aberrant urethral glands. Obviously, the squamous epithelium must have lost its point of origin.

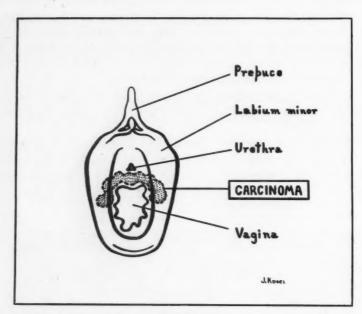


Fig. 2.—Diagram of external genitals, showing extent of involvement by carcinoma of the vesicovaginal septum.

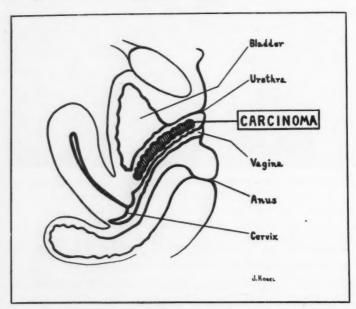


Fig. 3.—Diagram of sagittal section, showing extent of involvement by carcinoma of the vesicovaginal septum.

The Müllerian epithelium in the vaginal anlage becomes invaded and replaced by the epithelium of the urogenital sinus so that squamous-cell elements could be present.4, 5

The primary source of the carcinoma described in this report can only be determined by complete pelvic exenteration or postmortem examination.

Summary

- 1. A case history is presented of a 52-year-old patient with a carcinoma of the vesicovaginal septum and no readily evident source of the primary tumor. Treatment by supervoltage irradiation is described.
- 2. Possible points of origin, from the embryological standpoint, are mentioned.
- 3. The necessity of complete pelvic exenteration or postmortem examination for final determination of the site of origin of the primary tumor is stressed.

Addendum.—Since this report was completed, on March 21, 1955, a complete pelvic exenteration with colostomy and bilateral ureterostomy was performed because of advancement of disease.

It was still not possible to determine the primary site of origin of the tumor on pathological examination.

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255 SOUTH 17TH STREET

IS METHYLERGONOVINE TARTRATE SUPERIOR TO ERGONOVINE MALEATE?

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SINCE the advent of methylergonovine tartrate (Methergine), several studies have been published which are interpreted as proof of the superiority of this drug over ergonovine maleate (Ergotrate maleate). There is some question as to the validity of this interpretation.

Riordan and associates¹ presented data obtained from deliveries of 197 patients by 42 physicians using various obstetrical techniques. They measured as carefully as they were able the total blood loss during delivery. In 100 cases, 1 c.c. (0.2 mg.) of ergonovine maleate was given intravenously and in the other 97 cases, 1 c.c. (0.2 mg.) of methylergonovine tartrate was given intravenously. They stated that "bleeding was kept well below the accepted hemorrhagic level of 300 c.c. by both drugs" and concluded that methylergonovine is more effective than ergonovine. In their Table II, they separated the patients according to the amount of blood loss. In this table, the data for the entire series of patients indicate that 5 of 97 patients who received methylergonovine lost more than 300 c.c. of blood and only 3 of 100 patients with ergonovine lost such an amount. One patient who had methylergonovine lost 650 c.c. "without apparent reason."

Schade and Gernand² compared the effects of the two drugs in 956 patients. One cubic centimeter (0.2 mg.) of methylergonovine was given in 550 cases and an identical dose of ergotrate maleate was given in 406 cases. The distribution in so far as parity and method of delivery were concerned was essentially the same for the two groups. In their Table II, they report the distribution of anesthetic procedures. In basic form, these data are presented in Table I of this paper. The distribution is not homogeneous.

TABLE I. A TABLE PRESENTING THE DATA FROM TABLE II OF SCHADE AND GERNAND. THE NUMBER OF PATIENTS RECEIVING EACH COMBINATION OF TREATMENTS IS PRESENTED IN THE BODY OF THIS TABLE. THE DISTRIBUTION OF THE PATIENTS IS SIGNIFICANTLY HETEROGENEOUS

ANESTHESIA	METHYLERGONOVINE TARTRATE	ERGONOVINE MALEATE	TOTAL
Injection	350	171 .	521
Inhalation	200	235	435
Total	550	406	956

Chi square = 42.5, p = 0.005.

Therefore, any effects produced by differences in the anesthetic method may be reflected in the results with the oxytocics. Since injection anesthesia increases uterine tone and inhalation anesthesia decreases it, all interpretations must be made with great care. In spite of this obvious bias in favor of methylergonovine, the authors found that: (1) there was no significant difference in the two on measuring the time lapse between the first contraction and the end of the third stage of labor, and (2) a remarkable parallelism existed in the blood-loss curves.

TABLE II. THE DISTRIBUTION BY PARITY

PARITY	ERGOTRATE	METHERGINE	
0	11	10	
i	9	15	
ii	11	14	
iii	12	10	
iv	5	3	
v	2		

TABLE III. THE DISTRIBUTION BY AGE

AGE	ERGOTRATE	METHERGINE		
(YEARS)	(NO. OF PATIENTS)	(NO. OF PATIENTS)		
17	1			
19		2		
20	2	1		
21	4	2 1 3 3		
22		3		
23	1			
24	4	4 2 5		
25	5	5		
26		7		
27	4	3		
28	2	4		
29	4	1		
30	2	2		
31	2	4		
32		1		
33	2			
34	2	1		
35	2			
36	4 2 2 2 2 2 3	2		
37	3	1		
38	2	1		
39	ī	1		
40		2		
42		ī		
45	. 1	_		
Summary.—	•			
Sum of ages	1,462 years	1,414 years		
Number	50 patients	51 patients		
Mean age	29.2 years	27.7 years		
Standard deviation	±6.0	±5.8		

 $\begin{array}{lll} \text{Difference} & = & 1.52 \\ \text{Standard error of Difference} & = & 1.18 \\ \text{t} & = & 1.28 \end{array}$

TABLE IV. THE DISTRIBUTION OF TOTAL BLOOD LOSS (ESTIMATED AND MEASURED)

BLOOD LOSS				
(C.C.)	(NO. OF PATIENTS)	(NO. OF PATIENTS)		
20-49	6	5		
50-99	6	12		
100-149	9	13		
150-199	10	8		
200-299	10	7		
300-399	4	3		
400-499	2	1		
500-599	2	1		
600-699	1 1			
Summary.—				
Total blood loss	9,491 c.c.	8,008 c.c.		
Number	50 patients	51 patients		
Mean loss	190 c.c.	157 c.c.		
Standard deviation	±131	±129		

 $\begin{array}{ll} \text{Difference} & = 33.0 \\ \text{Standard error of Difference} & = 26.4 \\ \text{t} & = 1.25 \end{array}$

Forman and Sullivan,³ using patients with uncomplicated pregnancies, determined the frequency of occurrence of several undesirable side effects when slow intravenous injections of ergonovine or methylergonovine were given. They found that cerebral symptoms and thoracic symptoms were more common with methylergonovine. An increase in blood pressure was more common with ergonovine. Hamilton, Higgins, and Alsop⁴ found that severe vasomotor effects were most frequent with patients without premedication delivered under regional anesthesia. These responses were less frequent and less severe with premedication or in patients under general anesthesia. They observed no significant difference in blood loss with these two oxytocics in usual doses.

These and similar papers have led the Council on Pharmacy and Chemistry⁵ to state that the intensity and duration of the oxytocic effect of methylergonovine tartrate are somewhat longer and more intense than those of ergonovine maleate. This I believe to be an unwarranted assumption. The pressor effects with ergonovine may be somewhat greater than those with methylergonovine tartrate; however, since they are rare in normal patients not receiving an intravenous oxytocic during segmental anesthesia, they may be avoided. Segmental anesthesia is in itself oxytocic and intravenous ergonovine or methylergonovine is unnecessary. Subcutaneous injection is sufficiently rapid in these cases.

Method

One hundred and three consecutive patients delivered by one physician were given either 1 c.c. (0.2 mg.) of ergonovine maleate or 1 c.c. (0.2 mg.) of methylergonovine tartrate intravenously after expulsion of the placenta. The two groups of patients receiving different medications were essentially the same (statistically and clinically, there were no significant differences) in number, parity, method of delivery, and age. The total blood loss during the procedure was determined by measurement and estimation. Blood pressures were determined by the usual clinical method before medication and at ten minutes and one hour after administration of the oxytocic. Inhalation anesthesia was used throughout.

TABLE V. THE DISTRIBUTION OF CONTROL BLOOD PRESSURES

BLOOD PRESSURE	ERGOTRATE	METHERGINE	
(MM. HG)	(NO. OF PATIENTS)	(NO. OF PATIENTS)	
Systolic.—			
100-109	.3	3	
110-119	8	21	
120-129	17	12	
130-139	13	5	
140-149	4	4	
150-159	0	4	
160-169	2	. 1	
170	1	0	
Mean ± standard error	126.3 ± 3.8	123.3 ± 4.2	
Diastolic.—			
50-59	0	2	
60-69	16	11	
70-79	9	16	
80-89	12	12	
90-99	7	8	
100-109	1	0	
110-119	1	1	
120	1	0	
Mean ± standard error	77.9 ± 3.4	76.2 ± 2.8	

Results

The mean blood loss with ergonovine maleate was 190 with a standard error of \pm 19.4 c.c.; with methylergonovine tartrate it was 157 \pm 18.0 c.c. The difference between these means was not significant because of the large variation among patients. Actually 9 patients with ergonovine and 6 with methylergonovine were observed to lose 300 c.c. or more of blood. This difference in frequency was not significant. The greatest blood loss occurred in a patient who received methylergonovine (Table IV).

The change in blood pressure following the administration of the oxytocics was determined by subtracting the pretreatment value from each postreatment The mean differences are presented in Table VI. Obviously these changes have no clinical significance. When the distribution of these blood pressure changes was examined, and difference in the groups was observed.

TABLE VI. DISTRIBUTION OF CHANGE IN BLOOD PRESSURE (MM, HG)

	ERGOTEATE			METHERGINE					
CONTROL BLOOD	10 MINUTES 1		1 н	1 HOUR 10 MIN		NUTES 1 H		IOUR	
PRESSURE MINUS OB-	SYS- TOLIC	DIAS- TOLIC	SYS- TOLIC	DIAS- TOLIC	SYS- TOLIC	DIAS- TOLIC	SYS- TOLIC	DIAS- TOLIC	
SERVED BLOOD PRESSURE (MM. HG)	(NO. OF PA- TIENTS)								
-42	0	1	0	0	0	0	0	0	
-32 to -40	2	0	3	. 2	2	1	2	2	
-22 to -30	2	1	2	3	2	3	2	2	
-12 to -20	3	5	6	4	0	2	4	5	
-2 to -10	14	13	16	15	11	10	10	14	
+2 to $+10$	9	11	9	9	15	13	15	10	
+12 to +20	8	6	2	3	4	7	7	7	
+22 to +30	2	1	1	3	4	4	1	2	
+32	0	0	. 1	0	0	0	0	0	
Total	+2	-68	-190	-114	+84	+98	-24	+14	
Number	45	45	45	45	48	48	47	47	
Mean	0.04	-1.5	-4.2	-2.5	. 1.8	2.0	0.5	0.3	

Comment

It is stated in the literature that methylergonovine is a more potent oxytocic than ergonovine maleate. This, we believe, is predicated not upon fact but upon fantasy. The literature reviewed and the data from this study do not warrant this conclusion. The only possible conclusions follow.

Conclusions

- 1. When given intravenously in 1 c.c. (0.2 mg.) doses, ergonovine maleate and methylergonovine tartrate are equally potent.
- 2. Neither drug produced a significant change in blood pressure when given by the intravenous route to patients receiving a general anesthetic.

I wish to thank Dr. Charles M. Gruber, Jr., for the statistical analysis of the data.

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SQUAMOUS-CELL CARCINOMA OF THE CERVIX COMPLICATED BY MIXED SARCOMA OF THE UTERUS

Report of a Case*

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STUDIES of tumors of the genital tract, and particularly of the uterus, have been under way for many years with numerous investigators reporting diagnostic aids, incidence, treatment, and other interesting information.^{1, 2, 3}

It is well known that cancer of the cervix is the most common lesion of the generative tract and the region wherein most investigation has been con-The statistical studies of the radiation school versus the proponents of the surgical approach are well known and are a subject of ever continuing debate. More recently, studies of the adenocarcinomas and sarcomas have come more to the fore and their incidence and treatment have been discussed at length.4, 5, 6 Here in the United States, as the longevity of the adult woman reaches increasing heights as a result of good medical care and newer forms of therapy, people are being seen who have passed successfully the five-year barrier of treatment and are now confronted with the unbelievable situation of learning they have an entirely different neoplasm. In many clinics about the country, patients with cancer of two entirely different systems are under study and treatment. It is with these facts in mind that the following case is presented. It demonstrates an apparently cured case of malignancy of the cervix which was followed by death caused by a new disease of the generative tract.

Case Report

A 58-year-old woman, gravida i, para i, reported at the Outpatient Clinic of this hospital on June 15, 1953, with a history of pain in the right lower quadrant of six months' duration, which was described as sharp and twisting in nature. The cervix appeared normal, but the os was dilated 1.5 cm. The uterus was the size of a three-month pregnancy and the adnexa were clear. There were no signs of bleeding nor had there been any unusual bleeding. The past history was very interesting in that she had sought medical advice for intermenstrual spotting during 1946. The pelvic examination at that time revealed a fundus which was in midposition and perhaps slightly enlarged, normal in consistency, with some fixation. The cervix appeared clear; however, manipulation with an applicator caused bleeding. The adnexa were clear. A fractional type of diagnostic dilatation and curettage was done, the cervix and endometrium being curetted separately. On dilation of the cervix an endocervical polyp was found. The pathologic diagnosis returned was: (1) endometrium, showing mild hyperplasia; (2) squamous-cell carcinoma, Grade II, of the cervix (Fig. 1);

^{*}The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

and (3) endocervical polyp, showing squamous-cell carcinoma. She was treated with approximately 6,600 mg. hr. of radium, including some intracavitary radium. She had been seen at this hospital in 1950 with a pain in the right upper quadrant, at which time a diagnosis of cholelithiasis was made.

Because of the present complaint and findings, she was admitted on June 22, 1953, and a diagnostic dilatation and curettage were performed when the internal os of the uterus was dilated, about 1.5 c.c. of serosanguineous fluid escaped, and a tentative diagnosis of pyometra was made. The fluid was sent to the laboratory for cytologic study and culture. A mushroom-type catheter was inserted into the uterine cavity to permit further drainage. An examination under anesthesia failed to reveal any unusual pathologic condition except for the previously mentioned enlarged uterus. The cytologic study failed to produce evidence of malignancy, although a tentative diagnosis of uterine malignancy was made. Following this dilatation and curettage the patient ran a steady febrile course with signs of parametritis. She responded to repeated transfusions and erythromycin therapy after developing a severe urticaria, probably on the basis of a sensitivity to penicillin and streptomycin. As time progressed the size of the uterus remained the same.

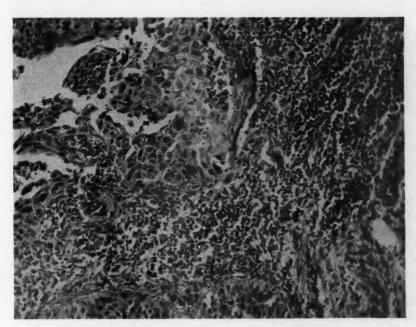


Fig. 1.—Squamous-cell carcinoma of the cervix, invasive.

On July 7, 1953, the patient was considered ready for further surgical intervention and a second diagnostic dilatation and curettage were done. On this occasion about 250 c.c. of rubbery, necrotic tissue were removed. In a few places the tissue was removed fresh and this was sent to the laboratory. On July 12, 1953, she again developed a low-grade fever and was noted to be developing jaundice. The serum bilirubin was 5.5 mg. per cent and thymol turbidity, 6 units. A diagnosis of homologous serum jaundice was made but fever, jaundice, and other symptoms promptly disappeared. On July 16, 1953, the Pathology Service, on the basis of exhaustive studies of the tissues removed during the dilatation and curettage, reported the diagnosis as mixed sarcoma of the uterus or mixed mesodermal sarcoma (Fig. 2). The tumor workup, which included intravenous pyelograms, cystoscopies, proctologic examinations, bone survey, x-ray of the chest, gastrointestinal studies and barium enema, failed to reveal evidence of metastasis; therefore on July 31, 1953, an exploratory laparotomy was done. She was found to have a frozen pelvis with tumor invading the

periaortic lymph nodes, the bowel being bound into the large tumor mass. On Aug. 18, 1953, deep x-ray treatment to four ports was begun and she received a total of 11,200 r in air. The patient was then sent home for terminal care.

On Dec. 1, 1953, she returned to the hospital with signs of large bowel obstruction and a transverse colostomy was performed. On Dec. 14, 1953, she died and the findings at autopsy were as follows: "Mixed sarcoma of the uterus with local pelvic metastasis, small and large bowel obstruction, obstruction of both ureters, and metastasis to the liver."

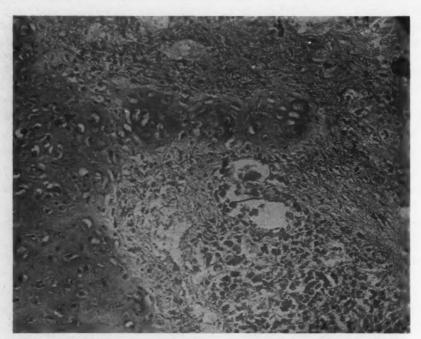


Fig. 2.-Mixed mesodermal sarcoma of the uterus.

In 1948, Lisa? reviewed the literature and reported on cases of carcinosarcoma of the body of the uterus but found no tumors wherein the entities arose from separate portions of the uterus. It is desired to add the case reported here to that of Kukla,8 who reported a case of adenocarcinoma of the cervix and the mixed mesodermal sarcoma occurring at the same time. Ours is believed to be the first case reported wherein a patient had squamouscell carcinoma of the cervix, League of Nations Stage I, apparently with a five-year cure, only to succumb to a mixed mesodermal tumor.

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GENERALIZED PERITONITIS FROM RUPTURED SIMPLE ULCER OF THE CECUM COMPLICATING THE PUERPERIUM: A CASE REPORT

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SIMPLE ulcer of the cecum was first reported by Cruveilheir¹ in 1830, but its occurrence is so rare that in the ensuing hundred and twenty-odd years very little has been learned about the condition, and most references to it in the literature are single case reports. Harrison² states that by definition simple ulcers of the cecum are those not associated with tumors, chronic ulcerative colitis, generalized arteriolar diseases of the gastrointestinal tract, or infection by specific organisms. Lipton and Reisman³ were able to collect only 84 cases of simple ulcer of the cecum from the literature up to 1951 and reported two of their own. Of these, 66 per cent showed perforation at operation or autopsy. In some, the course was fulminating and perforation occurred suddenly with very little reaction around the ulcer. In others, the course was more chronic and considerable fibrous-tissue reaction occurred, forming a mass which was frequently mistaken for carcinoma.

The disease was reported in an age range of 18 to 70 years and was twice as common in men as in women. The etiology of the condition is entirely unknown. The major complications were perforation and hemorrhage. The most common preoperative diagnosis was acute appendicitis with perforation and the operative mortality was 40 per cent. The procedures used at operation varied from simple closure of the ulcer to right hemicolectomy, the latter being performed in those cases which simulated carcinoma. Since operation was performed in many of the cases before the advent of modern antibiotic therapy, the operative mortality should decrease in the future.

We have not been able to find any report of this rare disease occurring as a complication of pregnancy, labor, or the puerperium and therefore feel that the following case should be reported as a pathological rarity.

The patient, Mrs. M. B., No. 534024, aged 29 years, a white housewife, was admitted to the obstetrical department of Evangelical Deaconess Hospital on the service of Dr. F. N., at 12:40 a.m., June 19, 1953. She was a gravida iv, para iii, eight months pregnant. The membranes ruptured at home just before she started for the hospital. Immediately after rupture of the membranes, she began to bleed quite briskly from the vagina. Her temperature was 37.2° C., pulse 92, blood pressure 110/80. The physical examination on admission showed a well-nourished white woman, conscious and ambulatory. The head and neck showed no abnormal findings, the chest was symmetrical, the breasts normal and the heart and lungs normal. The abdomen showed a gravid uterus apparently term size. The fetus was in a vertex presentation in left occipitoanterior position. The fetal heart tones were in the left lower quadrant and of good quality. There was no tenderness for undue rigidity of the uterus.

Immediately after admission the patient began to have good regular contractions at five-minute intervals. The uterus relaxed well between pains. There were no abnormal findings elsewhere in the abdomen. With the onset of labor the bleeding largely sub-

sided. Dilatation progressed rapidly and what appeared to be a full-term viable baby was delivered at 3:34 a.m., four hours after admission, by low forceps, episiotomy, and Kristeller expression. The placenta was expressed by the Credé maneuver soon after delivery and showed an area of premature separation along one edge. The patient was given a drop ether anesthetic which she took poorly. There was considerable vomiting and immediately after delivery the abdomen was markedly distended. The operator said that the delivery was conducted rapidly both because of the bleeding and because the patient was taking the anesthetic poorly.

After transfer to the recovery room, the patient was given one unit of blood. At that time the blood pressure was 130/76, pulse 88, respiration 26. Postpartum bleeding was of normal amount. A second unit of blood was given later on the same day since examination after the first transfusion showed the erythrocyte count to be 2.2 million and the hemoglobin 68%. During the day following delivery, the patient felt quite well and had very few complaints except that abdominal distention continued.

About 3:00 a.m., June 20, or approximately 24 hours after delivery, there was considerable abdominal distension and the patient began to complain of generalized abdominal pain which was most severe in the right lower quadrant. There was no definite rigidity but there was marked tenderness all over the abdomen which was most acute in the right lower quadrant. Catheterization yielded 250 c.c. of clear urine. A rectal tube was inserted and prostigmin 1:2,000, 1 c.c. every six hours, was started at 9:00 a.m. This gave some relief. The patient's temperature ranged from 37 to 38.4° C., the pulse from 92 to 132, and the respiration from 20 to 28. Flat films of the abdomen showed "gas in the large and small bowel with no fluid present. The symptoms are those of a paralytic ileus." No films were taken in the upright position. A blood count that day showed the erythrocyte count to be 3.5 million and the hemoglobin 71 per cent.

On the second postpartum day, June 21, the patient's condition was approximately the same. The temperature was 37.7° C., pulse 112, respiration 28. There was considerable abdominal distension but the patient was up to the bathroom and at times stated she felt better.

On the third postpartum day, June 22, there was marked exacerbation of all the symptoms and the patient's condition deteriorated rapidly. She was given an enema which had to be siphoned off. In the afternoon her temperature was 39.4° C., pulse 134, and respiration 48. A duodenal tube was inserted and Wangensteen continuous drainage instituted. The patient had been on continuous antibiotic treatment from the onset. By the evening of this day she appeared toxic and extremely ill. She expelled a large amount of liquid fecal matter and flatus during the night, but there was no relief from the distension and the abdominal pain. The clinical picture was now that of full-blown generalized peritonitis.

On the fourth postpartum day, June 23, her condition deteriorated still more rapidly. Temperature, pulse, and respiration all rose precipitately and the patient was extremely toxic. She was placed in an oxygen tent and other nonspecific measures were instituted. The abdomen was distended and silent with no peristalis or borborygmus, pulse 168 and of poor quality. A blood count showed the erythrocyte count to be 4.2 million, the leukocyte count 5,500, and the hemoglobin 99 per cent. Urine examination showed high concentration and a trace of albumin. Parenteral fluid administration was approximately 3,000 c.c. per day, the last two days.

The patient died at 9:50 P.M. The case was signed out clinically as generalized peritonitis secondary to puerperal infection of unknown origin.

Autopsy, as reported by Dr. Victor Hirsch, showed an acute diffuse purulent peritonitis. The uterus was normal for the fourth postpartum day. There was a small, round, clean-cut perforation of the cecum about 0.5 cm. in diameter a few centimeters from the ileocecal junction. There were other acute ulcerations of the mucosa of the cecum. There were no other ulcerative lesions of the gastrointestinal tract. The entire bowel was markedly distended with fluid. There were also acute passive hyperemia and edema of the lungs, partial atelectasis of the lower lobes, acute nephrosis, and small focal hemorrhages of the adrenal glands.

The bases of the ulcers of the cecum showed moderate amounts of organizing fibrin, so it was thought that the ulcers antedated delivery.

Comment

In reconstructing the development of events leading to this woman's death, we feel that primarily she was unfortunate enough to go into labor with several acute ulcerations of the wall of the cecum. The rapid development of abdominal distention so frequently seen in obstetrical patients who are taking a general anesthetic poorly, plus the increased intra-abdominal pressure incident to vomiting, expulsive efforts, and Kristeller expression, probably raised the intraluminal pressure of the bowel sufficiently to perforate the pre-existing ulcer. Following this, the only possibility of saving her life would have been early laparotomy with closure of the perforation. There were two leads which, if followed up, might have led to early operation. X-ray films taken in the upright position might have shown free gas in the abdominal cavity and thus have called attention to a ruptured viscus. Also, in the first twenty-four hours following delivery, the pain and tenderness were most severe in the right lower quadrant. Interpretation of this as appendicitis might have led to early laparotomy which was the essential therapeutic procedure.

Since simple ulceration of the cecum is of such rare occurrence, the possibility of encountering a similar situation is very remote. The case, however, besides being a pathological rarity, does emphasize the necessity of being alert for complications in the puerperium due to pathological conditions in the gastrointestinal tract. Sandweiss and associates' reported a death during the puerperium due to rupture of a peptic ulcer, a much more common pathological condition and one which is reportedly on the increase among women. They reviewed the histories of 70,310 pregnant women delivered at five Detroit Hospitals during ten consecutive years, 1928 to 1937, and found only one death due to perforated duodenal ulcer during the puerperium. They were able to collect only 13 cases from the literature in which death during the puerperium was due to complications of gastric or duodenal ulcers. In 9 of these the cause was perforation of the ulcer resulting in peritonitis and in 4 it was hemorrhage. The correct diagnosis was seldom made and, most striking of all, not a single patient was operated on. This certainly re-emphasizes the need to be alert for complications originating in the gastrointestinal tract during the puerperium.

Conclusion

A case of maternal death during the puerperium due to perforation of a simple ulcer of the cecum is reported. The need of being alert for complications in the puerperium arising from lesions in the gastrointestinal tract is emphasized.

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Department of Reviews and Abstracts

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Selected Abstracts*

Deutsche medizinische Wochenschrift

Vol. 80, No. 1, January 7, 1955.

*Massenbach, W., and Mueller, K.: The Treatment of Pruritus Vulvae and Ani With Alcohol Injections, p. 16.

*Kepp, R. K., Hartl, H., and Mueller, K.: The Importance of Radiogold in Gynecological Radiation Therapy, p. 19.

Martius, G.: Results of Care of the Newborn in an Institution Under Medical Supervision, p. 21.

Massenbach and Mueller: Treatment of Pruritus Vulvae and Ani With Alcohol Injections, p. 16.

One hundred ninety-five cases with follow-up are reported. Ninety-two patients were cured, 67 improved, and 36 unimproved. It was attempted to limit the treatment to patients in whom no underlying condition such as diabetes mellitus could be determined. In all but 5 of the failures, a reason for pruritus was later determined. The treatment consists of injecting 96 per cent alcohol subcutaneously in multiple injections of 0.2 c.c. for a total of 6 to 8 c.c. through several needle punctures. The only complication reported is the formation of small abcesses in 42 cases.

WALTER F. TAUBER, M.D.

Kepp, Hartl, and Mueller: Importance of Radiogold in Gynecological Radiation Therapy, p. 19.

Two uses for radioactive gold are discussed: the intraperitoneal and local injection into tumor masses. The first use is disappointing. In ten cases of female genital tumors, radiogold was injected locally. Local cure was obtained with slough and secondary scarring. The gold is found to be carried in the lymph channels and, therefore, near-by lymph nodes are thereby irradiated. However, distant metastases are unaffected. Radiogold is particularly useful because of its short half life and short tissue depth.

WALTER F. TAUBER, M.D.

Edinburgh Medical Journal

Vol. 61, December, 1954.

*Dawson, E. K.: Fibrosing Adenosis: A Little Recognized Mammary Picture, p. 391.

Dawson: Fibrosing Adenosis: A Little Recognized Mammary Picture, p. 391.

The histology and clinical characteristics of this condition, which may cause difficulty in interpreting material obtained by biopsy, are discussed extensively. When the condition is unrecognized, a false diagnosis of malignancy may be made though it has no genetic connection with malignant growth. In older subjects, however, it may co-exist with carcinoma which develops as epitheliosis.

DAVID M. KYDD, M.D.

Geburtshilfe und Frauenheilkunde

Vol. 14, No. 7, July, 1954.

- *von Mikulicz-Radecki, F.: Treatment of Placenta Previa and Abruptio Placentae by Vaginal Cesarean Section, p. 581.
- von Schubert, E.: Intrauterine Infestation of the Fetus by Gas Bacillus Necrosis of the Maternal Vagina With Formation of a Cloaca. Recovery After Six Operations, p. 587.
- *Ennker, J.: Alimentary Causation of Megaloblastic Anemia During Pregnancy and the Puerperium, p. 594.
- *Fochem, K., Grünberger, V., and von Narik, G.: Soft-Tissue X-ray Demonstration of the Placenta, p. 603.
- Böttger, H.: Experiences With Directed Compression in Hysterosalpingography, p. 612.
- Bucholz, R., Dibbelt, L., and Schild, W.: Progesterone Formation in the Menstrual Cycle, p. 620.
- Paschen, H. W., and Röttger, H.: The Use of Phenothiazine Derivatives in Operative Gynecology, p. 636.
- Wied, G. L., and Suchowsky, G.: Long-time Effects of Testosterone in Females, p. 645.
- *Ufer, J.: Treatment of Climacteric Syndrome With Mixtures of Hormone Esters Over Long Periods of Time, p. 650.

von Mikulicz-Radecki: Treatment of Placenta Previa and Abruptic Placentae by Vaginal Cesarean Section, p. 581.

Over 50 years ago, Dührssen advocated the use of vaginal cesarean section for the treatment of placenta previa and abruptio placentae. This procedure, never fully accepted by obstetricians and gynecologists, has fallen into disrepute, and to a large extent has been abandoned in favor of the more obvious transabdominal approach. It is agreed, however, that abdominal cesarean section has many disadvantages, not the least of which are peritoneal infection and traumatic and hemorrhagic shock. These disadvantages are less marked with the vaginal approach. Therefore, the procedure has been revived. A comprehensive study of all cases of placenta previa and abruptio placentae was made at the Woman's Clinic at the University of Berlin. A total of 102 cases of placenta previa and abruptio placentae were treated by operative measures during the years 1945 to 1953. Of these, 28 were vaginal hysterotomies, the remainder abdominal sections. It was felt from a comparative study that, with a normal birth canal, better maternal and fetal results were obtained with the simpler procedure of the vaginal approach. The technique of the vaginal method is discussed and outlined in detail, together with its contraindications.

L. B. WINKELSTEIN, M.D.

Ennker: The Alimentary Cause of Megaloblastic Anemia During Pregnancy and the Puerperium, p. 594.

The symptoms, signs, therapy, and differential diagnosis of all anemias, including the megaloblastic types, that may develop during pregnancy are discussed. Observations were made which seemed to point to the development of these disorders during the second half of gestation. The preliminary stage of the megaloblastic type was found to be macrocytic in origin. In 95 cases of severe anemia of pregnancy, 23 per cent were of this group, of which almost half developed during the second half of the winter. Development was felt

to be due to dietary deficiency and the importance of folic acid was stressed. The author feels that the lack of this substance is the etiological factor for these types of anemia, and its addition to the diet for both prophylaxis and treatment is mandatory, especially during the latter part of the winter. Adequate therapy consisted of high vitamin additions to the diet which included 2 to 5 mg. of folic acid daily.

L. B. WINKELSTEIN, M.D.

Fochem, Grünberger, and Narik: Soft-Tissue X-ray Demonstration of the Placenta, p. 603.

Comparative x-ray studies of the pregnant abdomen, with and without various metallic filters, showed without question that the demonstration of both maternal and fetal soft tissues with the use of aluminum filters gives better and more distinct pictures. This is most true in the diagnosis of the size and location of the placenta, the demonstration of which is almost impossible without the use of this type of filter. At the beginning of this study, it was thought that the routine antenatal examination of all pregnant women should include such a soft-tissue x-ray for the determination of the placental site. This was abandoned, because of its impracticability and because of the possible effects of exposure of the fetus to the x-radiations. The procedure is mandatory, however, where placenta previa is suspected because of hemorrhage in the third trimester, or because of malposition of the fetus in cases where normal pelvic mensuration is present. The author feels that, with the technique outlined, positive diagnosis of placenta previa can be made, and that, with certain minor exceptions, all degrees of low implantation of the placenta can be accurately outlined. He also states that such x-ray studies are of inestimable value in the course and conduct of delivery. It is of especial importance that such x-ray evaluation can be used to exclude the diagnosis of placenta previa in conditions where differential diagnosis must be made with premature separation. The author describes his results in 50 cases. The advantages and disadvantages of the procedure are discussed in detail.

L. B. WINKELSTEIN, M.D.

Ufer: Treatment of Climacteric Syndromes With Mixtures of Hormone Esters Over Long Periods of Time, p. 650.

It has been found necessary in many cases of severe climacteric symptoms to give therapy over long periods of time. Combinations of estrogens and androgens were used as the therapeutic agents. Studies of the clinical response were made, as well as of the possible pathological results which might occur following the use of these hormones. The author found that the combination of the male and female hormones gave much more satisfactory responses than did either one alone. Furthermore, with the combinations used, no untoward gastrointestinal symptoms were noted, nor was any change in the vaginal cytology seen which might be indicative of estrogen pathology. Minimal uterine bleeding might occur. Therapy was maintained at high levels for as long as three to five weeks. The author feels therefore that the use of estrogens and androgens for control of menopausal symptoms is beneficial and without harmful effect.

L. B. WINKELSTEIN, M.D.

Vol. 14, No. 9, September, 1954.

Roth, F.: Report on 24 Cases of Breast Carcinoma, p. 773.

*Alex, R.: Skeletal Tuberculosis in Pregnancy, p. 785.

Cramer, H.: Variations in Size and Shape of the Nuclei in Vaginal and Cervical Smears in Suspicious Cases of Carcinoma, p. 792.

Huber, H., and Hörmann, G.: Hydatidiform Mole, p. 799.

Wernze, H.: Permiability of the Placenta After Hyaluronidase Action, p. 813.

Ehrlich, H.: Closure of an Inoperable Rectovaginal Fistula with "Pallavit," p. 820. *Grünberger, V., and Holkup, H.: Oxygen Content of Cord Blood in Normal and Asphyxiated Children, p. 821.

*Klees, E., and Schlagetter, K.: The Importance of Leukocyte Changes in Fetal Erythroblastosis, p. 826.

Horning, K., and Stürmer, K.: The Interruption of Pregnancy in Women With Pituitary Tumors, p. 834.

Jelinek, E.: Discussion of R. Gross's Paper, "The Usefulness of DHE as an Anti-spasmotic in Obstetrics," p. 838.

Kepp, R. K.: Discussion of Hartleib's Work, "New Ways to Treat Hyperemesis Gravidarum," p. 838.

Koenan, F. W., and Bremer, K.: Operative Contributions in Urinary Incontinence, p. 839.

Lorbeer, G.: Results of the Treatment of Vesicocele by the Abdominal Approach, p. 844.

Boschann, H. W.: Ten-year Cure in a Case of Uterine Carcinosarcoma, p. 846.

Briel, R.: Rare Cystic Lower Abdominal Tumor, p. 853.

Brunner, O.: Hemorrhagic Adnexal Infarction Resulting From Regional Vein Thrombosis, p. 856.

Heizer, H.: Extrauterine Pregnancy Following Supravaginal Hysterectomy, p. 859.

Alex: Skeletal Tuberculosis in Pregnancy, p. 785.

The relationship of tuberculosis (present or healed) of bones and joints to the allowance of, or continuation of, pregnancy is discussed together with case histories for illustration. Whether skeletal tuberculosis is a contraindication to pregnancy depends on two factors-the extent of the disease and the duration of the so-called cure. It was felt that after two years of proved inactivity of the tubercular lesions, there is no contraindication to the inception and maintenance of pregnancy, nor is there any marked difference in the management of the labor. For periods of time of less than two years, or in active cases, an exact prognosis of the spread or cure of the tuberculosis is not possible, whether or not pregnancy is present. It was demonstrated by the review of many case histories that the extent of the disease may remain the same, increase, or decrease as the result of the pregnancy. Therefore, in principle, there is no definite indication for therapeutic abortion, albeit the possibility of seriously endangering the life of the patient is present if pregnancy occurs while she is still under treatment. It was felt that women with skeletal tuberculosis, desirous of having children, should be dissuaded, but in those instances where pregnancy is already present, or where the disease is discovered during pregnancy, the management of each case must be decided on its own merits, as to whether the additional burden can be handled. This is especially true where the spine or large joints are involved.

L. B. WINKELSTEIN, M.D.

Grünberger, and Holkup: Oxygen Content of Cord Blood in Normal and Asphyxiated Children, p. 821.

Voluminous studies of the oxygen content of the blood from the umbilical cord were made. In the normally born child, blood was taken by syringe before the child gave its first cry. Examination of this blood yielded 4.65 volumes per cent from the umbilical artery and 10.54 volumes per cent from the umbilical vein. After the first cry had been given and respiration established, the corresponding values were 7.79 volumes per cent and 12.36 volumes per cent. In asphyxiated newborn children, it was found that the oxygen content was 2.88 volumes per cent in the artery and 6.39 volumes per cent in the vein. These values tended to decrease as long as the asphyxia continued and the cord connection to the baby remained intact.

L. B. WINKELSTEIN, M.D.

Klees and Schlagetter: Importance of Leukocyte Changes in Fetal Erythroblastosis, p. 826.

The problems of fetal erythroblastosis, both diagnostic and therapeutic, have been almost completely answered by the works of Landsteiner, Wiener, Levine, Coombs, etc. Almost all of the research, however, has involved the study of antibodies on the red cells, with minimal consideration of the leukocytic elements of the blood. A daily study of white cell counts and morphology in the newborn was done in two cases of erythroblastotic infants due to Rh incompatabilities. Toxic changes of the leukocytes have been noted many times previously, which changes were not thought, in the literature, to have great prognostic significance. In one case studied by the authors, however, these toxic manifestations were considered to be of vital prognostic importance since they paralleled the abnormal fetal weight curve and preceded the red blood cell changes. In the second case studied, the child died of erythroblastosis on the third postnatal day. In this case toxic manifestations in the white cells were noted, despite the fact that no clues as to the severity of the erythroblastotic state were present on either physical examination or blood counts at birth. The authors consider the anemia of erythroblastosis as only a partial symptom of the general damage to all of the mesenchymal tissues, and they point out that all the other partial symptoms, i.e., the toxic leukocyte changes, etc., have also to be considered, as far as both diagnosis and therapy as well as prognosis are concerned. L. B. WINKELSTEIN, M.D.

Irish Journal of Medical Science

Sixth Series, No. 349, January, 1955.

*FitzGibbon, Henry: Stress Incontinence, p. 18.

*Coffey, Victoria P., and Jessop, W. J. E.: Congenital Abnormalities, p. 30.

FitzGibbon: Stress Incontinence, p. 18.

The paper opens with a concise discussion of the anatomy of the pelvis "insofar as it concerns the urethra." The author next discusses the anatomical causes of stress incontinence and their relationship, if any, to parturition. A survey is presented of several often-used operations for curing this impairment of urinary function. It is stated that there is a five-year recurrence rate of 47 per cent in 300 Kelly or Bonney operations.

The author presents, in detail, his father's (Gibbon FitzGibbon) operation for stress incontinence. It is stated that the operation has been in continuous use by the Drs. Fitz-Gibbon for 30 years "with uniformly satisfactory results," but has never been previously published.

This vaginal operation is characterized by a "special stress suture," placed lateral to the external urethral meatus and anchored on the anterior surface of the cervix uteri. When this suture is tied the urethra "is pulled upwards and backwards behind the symphysis pubis for ½ inch or more from its former position below and slightly in front, and to be now directed downward." This correction of location and direction of the urethra is thought by the author to be essential for success. He does not, however, give any results of the thirty years' experience of his father and himself. The six figures are not of good quality nor do they make the procedure very clear.

SCHUYLER KOHL, M.D.

Coffey and Jessop: Congenital Abnormalities, p. 30.

A study of 12,552 births in Dublin in the period March 1, 1953, to May 1, 1954, showed 204 abnormalities in infants. This is an incidence of 1.63 per cent. The following abnormalities were found with the indicated frequencies: anencephaly 29.5 per cent; spina bifida 24.4 per cent; hydrocephaly 20.3 per cent; talipes 16.6 per cent; meningoceole 6.9 per cent; cleft palate 5.5 per cent; cleft lip 5.1 per cent; mongolism 3.7 per cent.

Many patients had multiple anomalies. Each mother was visited as soon after birth of the abnormal fetus as possible and a standard questionnaire completed. A random sample of mothers of normal children were also visited. Both groups were analyzed. The authors' conclusions are:

- 1. General Incidence.—The incidence of congenital abnormalities in Dublin from March 1, 1953, to May 1, 1954, was 1.6 per cent.
- 2. Distribution.—Anencephaly was the predominant abnormality. The sex incidence showed a preponderance of females to the extent of 6 to 1. Workers in other countries have not usually found a ratio greater than 3 to 1. The National Maternity and Coombe Hospitals showed a much higher incidence of anencephaly than the Rotunda.
- 3. Maternal Age and Parity.—The incidence of deformities increases with maternal age and the proportion of Mongols was higher in the older age groups. In first pregnancies anencephaly occurred relatively less frequently than other abnormalities.
- 4. Factors Affecting the Health of the Mother Adversely During Pregnancy.—The effects of excessive vomiting and accident, though suggestive, were not statistically significant. Of the illnesses, "influenza" was much more frequent in abnormal pregnancies than in the controls, especially during the first three months. When judged by clinical inspection there appeared to be a statistically lower level of nutrition in the mothers of abnormal babies than in the controls. The differences in the cases of hemoglobin and plasma protein concentration were not statistically significant but about one-third of all the mothers examined were below normal in both these respects.
 - 5. Heredity.—There was definite evidence of the influence of genetic factors.
- 6. Relationship of Specific Factors.—No significant relationship could be established in the case of the mother's previous medical history, the social status of the family, the mother's blood group or Rh type, or maternal syphilis.

SCHUYLER KOHL, M.D.

The Journal of Obstetrics and Gynaecology of the British Empire

Vol. 61, No. 5, October, 1954.

Law, R. G.: The Action of Hydergine in Normal Labour, p. 581.

*Garrett, William J.: The Effects of Adrenaline and Noradrenaline on the Intact Human Uterus in Late Pregnancy and Labour, p. 586.

Stern, D. M., and Burnett, C. W. F.: An Evaluation of Modern Treatments of Eclampsia, p. 590.

*Gibson, G. B.: The Immediate Prognosis in Toxaemia of Late Pregnancy, p. 602.

*Russell, C. Scott, and Abbas, T. M.: The Treatment of Hydramnios Complicated by Anencephaly, p. 610.

*Sutherland, Arthur M.: The Treatment of Tuberculous Endometritis With Streptomycin and Pas, p. 614.

Denniss, Richard G., Goldie, William, and Polson, Cyril J.: Amniotic Embolism. A Report of Two Fatalities, p. 620.

Calman, Roy M., and Gibson, John: The Bacteriology of the Puerperal Uterus, p. 623. *Bancroft-Livingston, George: Ovarian Survival Following Hysterectomy, p. 628. Tatford, E. P. W.: Ectopic Cervical Tissue in the Vagina, p. 639.

Scott, Jean M.: The Metabolism of Iron in Pregnant Patients Treated With Massive Drip Infusions, p. 641.

*Scott, Jean M.: Therapy in the Megaloblastic Anaemias of Pregnancy, p. 646.

Feeney, J. K., and Barry, A. P.: Hydrocephaly as a Cause of Maternal Mortality and Morbidity. A Clinical Study of 304 Cases, p. 652.

Towers, Robert P.: Post-menopausal Endometrial Tuberculosis. An Unusual Case With a Review of Previous Reports, p. 657.

Morrison, J. K., and Ealand, C. T. F.: Post Partum Genital Tuberculosis, p. 661.

- *Charatan, F. B., and Oldham, A. J.: Electroconvulsive Treatment in Pregnancy, p. 665.
- Foulkes, John F., and Fraser, Russell: Radioiodine Tests in a Case of Struma Ovarii, p. 668.
- Flanagan, M. B.: Malignant Neoplasms Peculiar to Foetal and Infant Life With a Report on Two Cases, p. 671.
- *Chalmers, J. A.: Thrombocytopenic Purpura in Pregnancy, p. 675.
- McKeown, Thomas, Gibson, J. R., and Dougray, T.: A Study of Variation in the Length of the Menstrual Cycle, p. 678.
- Bernstine, J. Bernard, Meyer, Arthur E., and Hayman, Harry B.: Maternal and Foetal Blood Estimation Following the Administration of Chloral Hydrate During Labour, p. 683.
- Stein-Werblowsky, Rachel: The Early Detection of Cancer of the Uterus, p. 686.
- McBride, John M.: The Normal Post-menopausal Endometrium, p. 691.

Garrett: The Effects of Adrenaline and Noradrenaline on the Human Uterus in Late Pregnancy and Labour, p. 586.

The author notes the confusion that prevails concerning the exact physiologic effect of epinephrine U.S.P. on the human uterus in labor. It is known that the commercially available epinephrine contains 15 to 20 per cent l-noradrenaline. In this study, pure l-adrenaline and l-noradrenaline were given to patients in late pregnancy or in labor in an attempt to show the effect of each drug on uterine contractions. A small hydrostatic balloon was placed into the uterus outside the membranes and connected to a manometer and a recording apparatus. Ten patients were given l-adrenaline intravenously. In each instance all large coordinated uterine contractions were inhibited. The amplitude was diminished and the frequency of the contractions was decreased during the administration of the drug. If given during labor, the relaxation between the inhibited contractions appeared to be incomplete. Following withdrawal of the drug a period of uterine stimulation occurred in all but one case. Ten patients were then given l-noradrenaline bitartrate. In each of these patients large coordinated uterine contractions were stimulated during the administration of the drug. The contractions increased in frequency and with smaller doses increased in amplitude. When larger doses were given the amplitude of the contractions decreased but the base line was raised. The author concludes that it is probable the sympathetic nerves in the human uterus produce both adrenaline and noradrenaline. Because of the different effect that these two substances have on the myometrium, it is understandable that atypical contractions or incoordinate contractions may occur if the liberation of adrenaline and noradrenaline from the nerve endings is not physiologically balanced.

STEWART A. FISH, M.D.

Gibson: Immediate Prognosis in Toxaemia of Late Pregnancy, p. 602.

If one considers that the prolongation of a toxemic pregnancy does not lead to late maternal sequelae, conservative treatment with bed rest, diet, and sedation may be employed. The question then arises as to the optimum time for termination of the pregnancy. The author has attempted to answer this problem by the study of 1,420 cases of toxemia of late pregnancy. Toxemia of pregnancy was found to occur in 16.7 per cent of the patients seen in the Royal Maternity Hospital, Belfast, from 1946 to 1953. Of these cases of toxemia, 32.1 per cent were considered mild, 45.4 per cent moderate, and 22.5 per cent severe. Eclampsia was included in the severe group. The criteria for classification of these cases are presented in detail. The problem of classification of chronic hypertension in pregnancy is also discussed. There were 4 maternal deaths in this series (0.28 per cent) and 2 of these were preventable since they were related to the use of bougies for surgical induction of labor. The other 2 deaths were due directly to toxemia. There were 1,516 total births, of which 84.1 per cent of the infants were living, 10.7 per cent were fresh or macerated stillbirths, and 5.2 per cent died in the neonatal period. The corrected

fetal wastage was 11.7 per cent. In the cases in which conservative treatment of toxemia of pregnancy was carried out an attempt was made to determine the stage of gestation at which optimal fetal survival was obtained. The analysis showed conclusively that until the thirty-fifth week of pregnancy conservative treatment is of benefit to the baby. After the thirty-fifth week, however, early delivery gives better fetal results and an attempt to allow the baby to mature in utero further increases the fetal mortality. Labor was induced by rupture of the membranes and apparently oxytocic drugs were not used. The author notes the statistical errors that affect any study of this type.

STEWART A. FISH, M.D.

Russell and Abbas: Treatment of Hydramnios Complicated by Anencephaly, p. 610.

This is a review of 201 cases of anencephaly complicated by hydramnios. Since anencephaly represents a form of biologic wastage, many individuals believe immediate termination of such a pregnancy is advisable. The patients in this series were divided into two groups. There were 93 cases in the surgical-induction group and 60 cases in the conservative-treatment group. These two groups were comparable in respect to age, parity, rate of onset of hydramnios, and history of previous obstetric abnormality. There were no complications in the surgical induction group in labor or during delivery. In the conservative-treatment group, the uterus of one patient ruptured spontaneously through an old upper segment cesarean scar at 34 weeks' gestation. The membranes were ruptured before the thirty-eighth week of pregnancy in all patients in the surgical-induction group and the remainder were allowed to go into labor spontaneously. The authors conclude that labor should be induced in patients with hydramnios complicated by anencephaly as soon as the diagnosis is established, since it shortens a useless gestation and leads to a smaller number of labor difficulties which require operative interference. Surgical induction showed a higher incidence of delay in delivery when attempted before the thirtysecond week of pregnancy, as might be expected. No oxytocic drugs were utilized in this series.

STEWART A. FISH, M.D.

Sutherland: Treatment of Tuberculous Endometritis With Streptomycin and PAS, p. 614.

This report represents the results obtained to date from an investigation undertaken in 1950 by a Joint Subcommittee representing the Royal College of Obstetricians and Gynaecologists and the Research Committee of the British Tuberculosis Association. A total of 109 patients with tuberculous endometritis were studied in this series. Of these, 57 were treated and 52 observed as a control group without treatment. All patients in the control series were checked at identical intervals to the treated group and were removed from the observation regime if active disease was encountered at the end of one year, if any clinical deterioration developed during the period of observation, or if it was felt it might be harmful to withhold treatment from the patient. No patient with active extragenital tuberculosis was included in the trial. Only 9 patients gave a history of previous pregnancy and 52 patients complained of infertility, the most common presenting symptom. Abdominal pain was present in 21 patients and irregular or profuse menstruation was present in 12. Ten patients complained of secondary amenorrhea. X-ray of the chest showed quiescent pulmonary tuberculosis in 32 patients. On pelvic examination 61 patients were normal and 47 showed a variable degree of adnexal thickening which was mostly bilateral. The diagnosis was based on histologic findings from curettings and bacteriologic proof was sought in each case. Positive cultures were obtained in 75 of the 109 cases. The human strain of tubercle bacilli was identified in 52 instances and bovine tuberculosis in 4. Treatment consisted of streptomycin (calcium chloride complex) by intramuscular injection for 84 consecutive days and 3 Gm. of para-aminosalicylic acid four times daily by mouth over the same period. All patients were ambulant throughout treatment and many continued work. In 4 instances it was necessary to discontinue treatment because of drug toxicity. Endometrial biopsy was performed in the middle and at the

end of treatment. This was repeated at three and six months after therapy. At the end of a year complete dilatation and curettage was carried out in order to ascertain the presence of residual tuberculosis. At the time of this report, 27 treated cases have been followed up to one year. Of these, 24 (89 per cent) showed no evidence of endometrial tuberculosis while the condition recurred in the remaining 3 patients. The effect of treatment on the adnexal disease was variable. Of the 3 patients who showed recurrence of infection after treatment, only one had tuboovarian masses. In the control group, 10 cases deteriorated clinically which necessitated removal from the series. Of these 10, 8 showed evidence of exacerbation of the disease in the pelvis, one developed activity of a quiescent chest lesion, and one developed tuberculous meningitis. This last patient recovered completely after an intensive course of streptomycin and PAS. Twenty-five patients in the control group have been followed one year or more and 20 of these showed residual tuberculosis. In the treated group, none of the patients have subsequently become pregnant which is not surprising. All menstrual disturbances have completely disappeared in the treated group and the 9 patients who complained of abdominal pain reported either complete relief or considerable improvement. The author concludes that one is not now justified in withholding treatment from any patient with proved tuberculosis of the endometrium.

STEWART A. FISH, M.D.

Bancroft-Livingston: Ovarian Survival Following Hysterectomy, p. 628.

Because of the disagreement among gynecologists as to whether the ovary should be preserved at the time of hysterectomy, this study was undertaken. There were 589 patients in this series who had undergone abdominal hysterectomy with conservation of ovarian tissue. Ovarian function was estimated by means of vaginal smears taken at frequent intervals following operation. The series was divided into two groups. The first group was operated on before the age of 45 and the second group after the age of 45. A control group of women of comparable age with normal pelves was utilized. After three years, 5 per cent of the younger patients had atrophic smears which suggested ovarian failure. After five years this figure had risen to 40 per cent. The author notes that the presence or absence of hot flashes bears little relation to ovarian survival as reflected in the vaginal smear, since a number of women with active smears suffered from vasomotor phenomena and an almost equal number with inactive smears had no symptoms at all. Of the patients operated on over the age of 45, 25 per cent showed inactive smears three years after operation and this level rose to 78 per cent after more than five years. It is noted that estrogen from the adrenal may affect the vaginal smear. The author concludes that the operation of hysterectomy with conservation of ovarian tissue does nothing to hasten the onset of ovarian failure or menopausal symptoms. He also believes that ovarian conservation should be practiced at hysterectomy at any age since the ovaries continue to function for a considerable period of time as evidenced by the vaginal smear. No evidence of ovarian cyst or ovarian carcinoma was found in any of these patients following hysterectomy.

STEWART A. FISH, M.D.

Scott: Therapy in the Megaloblastic Anaemias of Pregnancy, p. 646.

This interesting paper on megaloblastic anemias of pregnancy deals with 37 cases, 19 of which were treated in the antenatal period and 18 in the postpartum period. Vitamin B_{12} , crude liver, and folic acid were the agents utilized. The diagnosis was made by sternal puncture in 26 of the cases and in the remaining 11 the typical megaloblasts which were found in the peripheral blood were diagnostic. The peripheral blood smears were normocytic or microcytic in one-third of the patients. In these individuals it was difficult to make the diagnosis without sternal puncture because typical megaloblasts were often not found in peripheral blood. The author noted that after a few injections of intravenous iron the red cells of these patients tended to become macrocytic and within a few days typical megaloblasts appeared in the blood films. This made it possible to

establish the diagnosis in those individuals in whom sternal puncture could not be carried out. When the diagnosis was made early in the antenatal period and treatment instituted, the mortality and transfusion rates of the patients were greatly reduced. There were no deaths in the present series. In a previous series reported from the same hospital there were 2 deaths in a group of 30 patients. In this report vitamin B₁₂ produced a temporary improvement, but subsequently the condition tended to relapse and the marrow picture showed a more pronounced failure of maturation. Parenteral liver therapy produced a relatively normal blood picture in some instances but the majority of the patients did not improve. Folic acid was the treatment of choice. All patients in the ante and postnatal period returned to normal even when the bone marrow showed marked immaturity of cells. There was some delay in the improvement of the peripheral blood picture in a few instances, however. One patient developed a rash after intravenous folic acid. There were no other evidences of drug toxicity. In addition to folic acid all patients should be given additional iron. It is thought that the action of folic acid is related to the maturation of the earlier stages of erythropoiesis whereas vitamin B12 is more concerned with the later phase of the process. The author suggests that megaloblastic anemias of pregnancy may be due to malabsorption of folic acid from the gastrointestinal tract or inability of the body to split folic acid conjugates.

STEWART A. FISH, M.D.

Charatan and Oldham: Electroconvulsive Treatment in Pregnancy, p. 665.

The authors report a case in which six electroconvulsive treatments were given to a schizophrenic woman from the twenty-eighth to the thirty-first week of pregnancy. Intravenous Pentothal and Suxethonium were given concomitantly to modify the convulsion. The patient went to term and delivered a normal infant. No uterine contractions were observed either during or following any of the convulsive episodes. The authors review the literature concerning this problem and note 2 instances in which fetal death occurred when electroconvulsive treatment was combined with insulin shock in the first five months of pregnancy.

STEWART A. FISH, M.D.

Chalmers: Thrombocytopenic Purpura in Pregnancy, p. 675.

The author reports 6 cases of idiopathic thrombocytopenic purpura in pregnancy. By 1951 only 22 true instances had been reported in the medical literature. In 3 of the presently reported cases purpura was seen only during pregnancy, which was probably related to increased circulating estrogen. Postpartum uterine hemorrhage occurred in only one patient. Excessive blood loss occurred from the episiotomy in one patient, however, and the author suggests that surgical incisions be avoided. The thrombocytes play a large role in the control of bleeding from lacerations or incisions and a small role in control of bleeding from the postpartum uterus. Splenectomy was not performed during pregnancy in any of these cases and may usually be avoided by the use of ACTH, cortisone, and blood transfusion. The prognosis of thrombocytopenic purpura and pregnancy is usually good when fresh whole blood is given during labor and surgical incisions and tears are avoided.

STEWART A. FISH, M.D.

The Medical Journal of Australia

Vol. 1, No. 2, January 8, 1955.

*Burnett, R. Kent: Post-Maturity, p. 40.

Burnett: Post-Maturity, p. 40.

This is a review of some of the current literature on the controversial subject of postmaturity. There are a number of investigators quoted who refuse to accept post-

maturity as a true syndrome. Dr. Burnett, however, is inclined to agree with the findings of James Walker and Dudley Racker, proponents of the theory of postmaturity.

Dr. Walker has published a convincing study on fetal anoxemia in the British literature. Dr. Racker's work is discussed in greater detail. The latter's investigation involved 1,220 deliveries used as a controlled series in which there were 19, or 1.54 per cent, stillbirths, 203 women in whom labor was induced at term and who sustained 3 stillbirths, or a rate of 1.4 per cent, and 410 women comprising the postmature group, who had 19 stillbirths, or 4.63 per cent. (This last figure is incorrectly stated as 1.63 per cent in the journal.)

The last group is further subdivided into deliveries less than fourteen days after the expected date of confinement and those seven to fourteen days postmature. The stillbirth rate in the former was 8.72 per cent and in the latter 2.31 per cent. There is a statistically significant difference between these figures and the fetal mortality in the group with induced labor.

The conclusions are that the stillbirth rate increases markedly after the forty-third week of gestation, that this rise is due to unexplained causes, and that fetal distress in infants of both primigravidas and multiparas is more common after the fortieth week. These are essentially the conclusions of James Walker.

ARTHUR PERELL, M.D.

Vol. 1, No. 3, January 15, 1955.

*Hardcastle, E. J. B.: Deep X-ray Therapy in Gynecology, p. 68.

Hardcastle: Deep X-ray Therapy in Gynecology, p. 68.

This is a brief but comprehensive discussion of the various gynecological conditions treated by deep x-ray therapy. There are three factors responsible for failure: the patient is obese, so that adequate dosage cannot be administered; the patient is too weakened by her chronic disease to tolerate radiation; or the tissue is not radiosensitive. Supervoltage radiation may be the solution to these problems.

In cases of secondary amenorrhea gratifying results have been produced by the produced by roentgen therapy in cases of carcinoma of the breast, functional uterine bleeding, leiomyomas of the uterus, and selected cases of endometriosis. The advantages of exposure of the ovaries to nonsterilizing doses of x-ray. Artificial menopause has been deep x-ray therapy over radium insertion are considered.

Dr. Hardcastle discusses gynecological malignancies and compares surgical and x-ray treatment for each. Carcinoma of the vulva is difficult to treat by any method. This area readily undergoes necrosis when therapeutic radiation is administered. Surgery is probably the best primary treatment and x-ray should be reserved for treatment of discharge and spread.

The therapy in urethral cancer depends upon the location of the lesion. Prognosis in vaginal carcinoma is poor, with less than 20 per cent five-year cures in even the better centers.

Various aspects of x-ray treatment of cervical carcinoma are considered at length, with the conclusion that both surgical and radiological treatments produce the same percentage of successful cures. Uterine and ovarian malignancies should be treated by extirpation and subsequent radiation.

In conclusion the author briefly discusses some common complications of radiation treatment. This monograph is a valuable survey of the general topic and lacks only a bibliography to make the article a complete one.

ARTHUR PERELL, M.D.

Correspondence

Traumatic Vulvar Hematomas

To the Editors:

In reference to the six cases of traumatic vulvar hematoma reported by John J. Hudock and associates in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, November, 1955, page 1064, I would like to describe another case, which I saw in Bagata, Belgian Congo, in April, 1955.

W. M., an 18-year-old Negro woman, four months pregnant, was carried to the hospital some six hours after she had slipped while crossing a little stream, and fallen astraddle of a small tree. She was found by her relatives, having sustained heavy loss of blood, and taken to the hospital. By the time she was admitted to the emergency room, she was in deep shock and presented a syndrome of acute anoxemia. She was immediately given a transfusion of plasma and an injection of a stimulant.

Upon examination I noticed a large, diffuse, bluish hematoma, involving the entire right labium majus, labium minus, clitoris, and vaginal wall. Whenever the labia were separated for examination, blood and clots gushed out of a small laceration of the vulva, about a quarter of an inch in length, just to the right of the orificium urethrae. Owing to the hematoma and the tenderness of the tissues it was impossible to insert a catheter into the bladder. After most of the clots were removed, the vagina was tightly packed and a pressure dressing applied.

At one point the woman appeared nearly dying. She was delirious, heavily agitated, and showed severe dyspnea. She was given another transfusion of 500 ml., and antibiotics (penicillin and streptomycin), and kept in Trendelenburg position on the table for the next six hours. After she became conscious and seemed to have improved a little she was cautiously transferred to bed and an ice bag was applied. The next day she was much better and a catheter was successfully inserted in the urethra.

The patient continued to improve. The fourth day the vaginal pack was removed and the following day the catheter. After a week she was allowed to walk and was dismissed from the hospital after another week. Pregnancy continued and she was uneventfully delivered last September of a normal girl baby.

DR. J. A. M. E. BURKE

DIRECTION FOREAMI LEOPOLDVILLE, BELGIAN CONGO DECEMBER 28, 1955

Spontaneous Subarachnoid Hemorrhage

To the Editors:

The article by Samuel P. Fleming, M.D., and Charles H. Mauzy, M.D., in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, volume 70, page 1133, 1955, in which they mentioned 32 cases in the literature of spontaneous subarachnoid hemorrhage complicating pregnancy, prompts me to add briefly two more cases. These patients were delivered at the Community Hospital in Glen Cove, Long Island.

Mrs. H. F., No. 108542, a 35-year-old multipara, was referred to me for "delivery by section" by the neurologist who cared for her at the Nassau County (Meadowbrook) Hospital

where she was a patient from Dec. 22, 1954, to March 12, 1955, with a diagnosis of spontaneous subarachnoid hemorrhage. She was delivered on June 17, 1955, without difficulty, by easy outlet forceps. Her postnatal course was uneventful.

Mrs. E. B., No. 91376, a primipara 45 years of age, suffered a spontaneous hemorrhage on Sept. 11, 1953, shortly after the end of a cesarean section which was done because of failure to demonstrate progress after 12 hours of labor with ruptured membranes for 16 hours. Several hours after the operation, which was done under spinal anesthesia, there was spastic paralysis of the entire right side. After a stormy course, the patient was discharged with residual weakness of the foot and hand. Six months later, all this had disappeared except for very slight weakness of the foot.

ROBERT S. MILLEN, M.D.

WESTBURY LONG ISLAND NEW YORK JANUARY 6, 1956

The Etiology of Pre-eclampsia

To the Editors:

Obstetricians everywhere must be grateful to Drs. Dieckmann and Pottinger for the valuable data provided in their paper on the Etiology of Pre-eclampsia-eclampsia, Am. J. Obst. & Gynec. 70: 822, 1955.

Their striking results emphasise the marked changes in the extracellular and especially the intracellular content of water and electrolyte and inadvertently create the impression that these are primarily responsible for the syndrome. Primary concern must still lie with the mechanism responsible for the retention of water and electrolyte and not with their transfer from one body compartment to another or their increased presence within the cell, which merely precipitates the eclamptic onset.

In proceeding to explain this retention, the authors advance three mechanical causes—increased intrauterine, increased intra-abdominal, and increased inferior vena caval pressure. But none of these could explain the recurrence during subsequent labour of toxaemic signs after their abatement intra partum on the death of the foetus. Nor could they explain postpartum eclampsia, while the absence of pre-eclamptic toxaemia when large fibroids, ovarian cysts, or gross ascites are present should deny aetiological significance to increased intra-abdominal or inferior vena caval pressure.

The authors next proceed to postulate a prerenal deviation of salt and water in explanation of the oedema, and claim in the first instance that increased venous pressure in the legs, dependent on the mechanical causes already enumerated, effects this retention. But the fact that neither large nonmalignant pelvic tumors nor gross ascites produce like changes is against this view. Increased permeability of the capillaries is next advanced. However, the range of the osmotic tension of the oedema fluid when carefully obtained contradicts the contention.

Finally, disordered renal function is incriminated for the salt and water retention. This, the established occurrence of reduced glomerular filtration fully substantiates. A 1 per cent reduction in its rate accounts for the daily retention of 11 Gm. of sodium. A diminished renal blood flow is held to underlie this change, and it is against the thesis of its production that my paramount criticism is directed. The theoretical explanation for its occurrence put forward by the authors is that all body functions are dependent on intracellular concentrations of water and electrolyte and it is to these that the various signs and symptoms can be correlated. Testing the effects of the alterations of concentrations by applying methods of actual measurement, their argument cannot be supported. Their data indicated that the intracellular sodium and hence the state of hydration of the cell was lower in pre-eclampsia than in the normal pregnant state. Yet according to Tobian and Binion²

it is overhydration that effects a reduction in glomerular filtration for they found in the renal arteries of hypertensive patients a 22 per cent higher sodium content and a 17 per cent higher water content that augmented the flow resistance by 50 per cent in these vessels. It is evident that neither pressure, prerenal deviation, nor the state of cellular hydration is responsible for the primary retention of salt and water for which I have advanced the following theory.

Reduction of the glomerular filtration rate is intrinsic in renal cortical ischaemia which the uterorenal reflex has been shown to evoke, while the degree of resistance the myometrium displays to stretch is commensurate with the renal response. Herein, in the human, the toxaemic aetiological significance of the primigravid state of hydramnios, of multiple pregnancy, of concealed rather than revealed accidental haemorrhage, and of the corollary provided by the therapeutic value of rupture of the membranes finds explanation, while in the animal the uterus by its ability to "convert" protects it against stretch effects and consequently confers immunity against toxaemia. Heightened isometric tension, an oestrin influence, may well underlie the association of pre-eclampsia with hydatidiform mole, which rapid growth also serves to explain. Finally, uterine contractions post partum have been observed in animals to provoke renal cortical pallor and offer an explanation of the culmination of pre-eclampsia in eclampsia post partum.

Much evidence is available to show that the primary retention is thus effected, while Dr. Dieckmann and Dr. Pottinger's data have indicated the final stages of its handling terminating

My purpose in this communication is to distinguish the primary from the secondary effects and enjoin that in the first place our therapeutic efforts should be directed to the former.

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 Tobian, L., Jr., and Binion, J. T.: Circulation 5: 754, 1952.

JOHN SOPHIAN, F.R.C.S. (ENG.), M.D. (LOND.), M.R.C.P. (LOND.), M.R.C.O.G.

66 HARLEY STREET LONDON, W.I. OCTOBER 28, 1955

Reply by Dr. Dieckmann

To the Editors:

We appreciate Mr. Sophian's comments. He has taken for granted certain statements, based on published reports, which were meant to be comments. We have no preconceived ideas of the etiology of pre-eclampsia which we are trying to prove. We have been accumulating data for many years about pre-eclampsia-eclampsia which we hope will eventually lead to an explanation of its cause. There is no need to explain why pre-eclampsia does not occur with large ovarian cysts, myomas of the uterus, etc.; there is no placenta. True pre-eclampsia rarely, if ever, recurs; primiparity which is essential can occur only once.

> WILLIAM J. DIECKMANN RUSSEL POTTINGER

CHICAGO, ILLINOIS **DECEMBER 12, 1955**

Item

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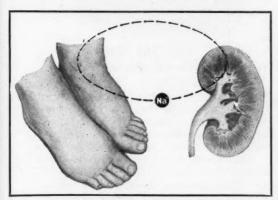
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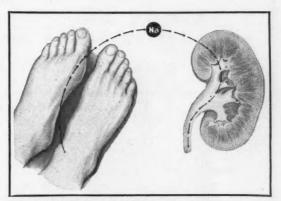
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No. 2

Edited by

F. HOMBURGER, M.D., and W. H. FISHMAN, Ph.D.

Research Professor of Medicine and Research Professor of Biochemistry and Nutrition, Tufts University School of Medicine, Boston, Mass.

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Introduction

By F. Homburger, M.D., and W. H. Fishman, Ph.D., Director and Associate Director of the Cancer Research and Cancer Control Unit, Tufts University School of Medicine, Boston, Mass.

The Epidemiology of Cancer of the Cervix

By E. LOMBARD, M.D., Director, Division for Cancer and Chronic Diseases, Department of Public Health, Commonwealth of Massachusetts

A Gynecologist's Evaluation of Methods of Early Cancer Diagnosis

By Paul A. Younge, M.D., Associate Chief Surgeon Free Hospital for Women, Brookline, Mass.

Fundamental Studies of the Cell, Observations Underlying the Concept of Cancer Cell Detection by Automatic Scanning Microscopes

By ROBERT C. Mellors, M.D., Ph.D., Associate Member, Sloan Kettering Institute for Cancer Research, New York, N. Y.

The Cytologic Prognosis of Cancer of the Cervix Treated by Radiation

By RUTH M. GRAHAM, Vincent Lab., Massachusetts General Hospital, Boston, Mass.

Cytologic Prognosis in Cancer of the Cervix Treated by Surgery or Radiation

By JOHN B. GRAHAM, Vincent Lab., Massachusetts General Hospital, Boston, Mass.

Beta-Glucuronidase in Cancer Diagnosis and Endocrinology

By W. H. Fishman, Ph.D., Associate Director of the Cancer Research and Cancer Control Unit, Tufts University School of Medicine, Boston, Mass.

Clinical Applications of Vaginal Fluid Beta-Glucuronidase

By S. C. Kasdon, M.D., Associate Clinical Professor of Gynecology, Tufts University School of Medicine, Boston, Mass.

Discussion of the Papers on B-Glucuronidase

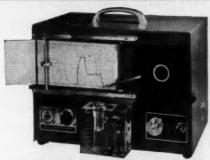
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> RIGHT: Nu-Lift supported Pregnancy: Baby is elevated, body is erect, intra-pelvic pressure lessened. Bulging, stretching minimized, backache relieved, possibil-ity of varicosities lessened.

* PATENT #2,345,760



MATERNITY Nu-lift SUPPORTS and brassieres

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The illness starts like any other febrile attack. But soon the face is flushed. There is high fever. After two or three days, the pulse becomes feeble, the skin cold and of a lemon-yellow tint. Chances of recovery hardly approximate 50%.

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And she, who had fearlessly nursed the worst fever cases, thought undergoing the disease herself would make her a better nurse. She asked to be bitten by an infected mosquito. "I tried to dissuade her," said the medical director. "But she insisted."

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- Mycotic Leukorrhea
- Diabetic Vulvitis
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PHYSICIANS PREFER Gentian Violet Supprettes because maximum fungicidal activity is assured by thorough dispersion of the medication throughout the vaginal area.

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